



Cited

Europäisches Patentamt

European Patent Office

Office européen des brevets

Publication number:

0 337 549

A1

(3)

## EUROPEAN PATENT APPLICATION

(2) Application number: 89200864.0

(5) Int. Cl.: C07D 205/08 , A61K 31/395

(6) Date of filing: 06.04.89

(7) Priority: 11.04.88 US 179688

(4) Date of publication of application:  
18.10.89 Bulletin 89/42

(5) Designated Contracting States:  
AT BE CH DE ES FR GB GR IT LI LU NL SE

(7) Applicant: MERCK & CO. INC.  
126, East Lincoln Avenue P.O. Box 2000  
Rahway New Jersey 07065-0900(US)

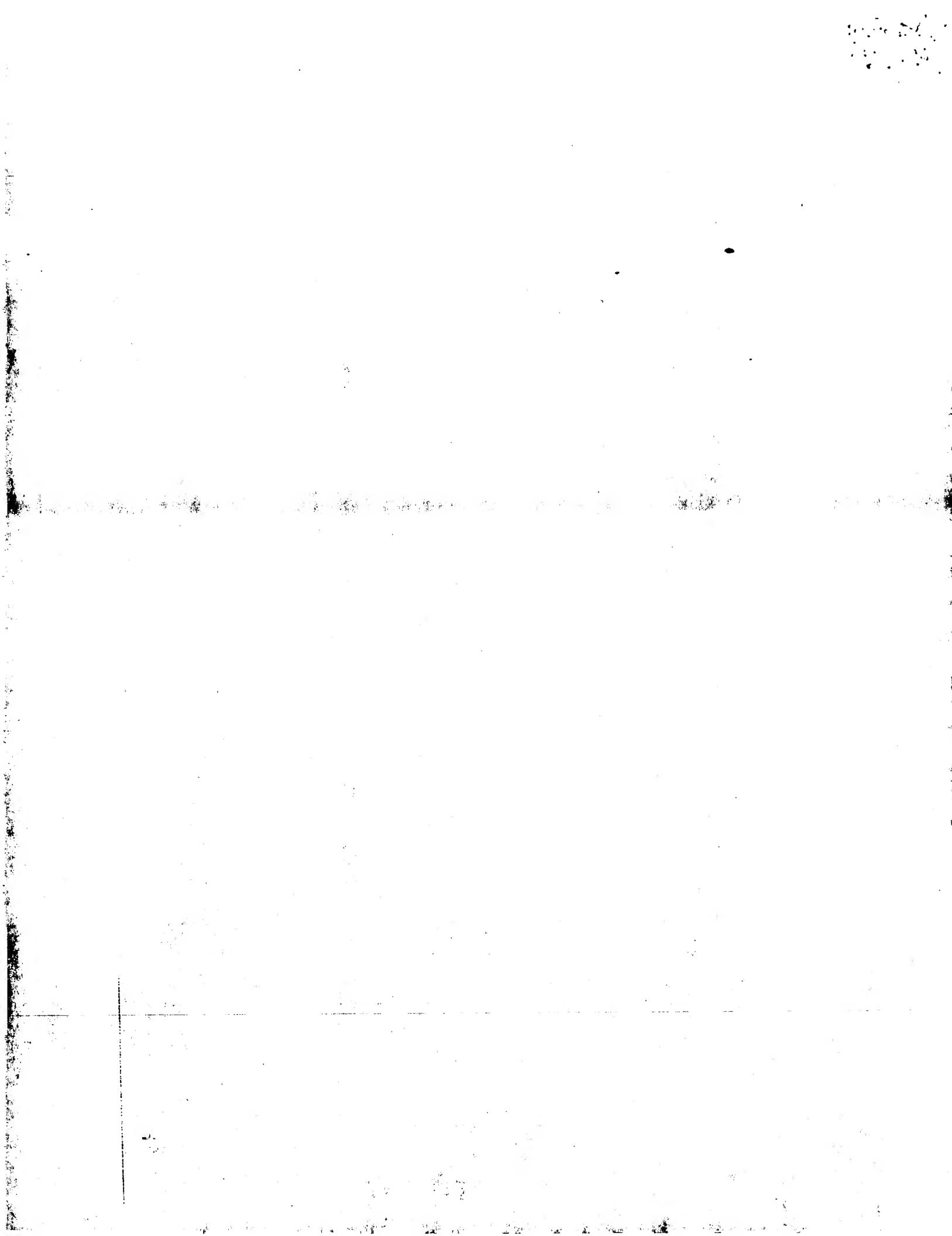
(7) Inventor: Shah, Shrenik K.  
25 Denise Court  
Metuchen New Jersey 08840(US)  
Inventor: Finke, Paul E.  
34 Inwood Drive  
Milltown New Jersey 08850(US)  
Inventor: Doherty, James B.  
559 Columbia Street  
New Milford New Jersey 07646(US)  
Inventor: Barker, Peter L.  
518 Hort Street  
Westfield New Jersey 07090(US)  
Inventor: Hagmann, William  
309 Hyslip Avenue  
Westfield New Jersey 07090(US)  
Inventor: Dorn, Conrad P.  
972 Fernwood Avenue  
Plainfield New Jersey 07062(US)  
Inventor: Firestone, Raymond A.  
387 Temple Street  
New Haven Connecticut 06511(US)

(7) Representative: Hesketh, Alan, Dr.  
European Patent Department Merck & Co.,  
Inc. Terlings Park Eastwick Road  
Harlow Essex, CM20 2QR(GB)

(1) New substituted azetidinones as anti-inflammatory and antidegenerative agents.

(9) New substituted azetidinones are found to be potent elastase inhibitors and thereby useful anti-inflammatory/antidegenerative agents.

SEARCHED



## NEW SUBSTITUTED AZETIDINONES AS ANTI-INFLAMMATORY AND ANTIDEGENERATIVE AGENTS

BACKGROUND OF THE INVENTION

We have found that a group of new substituted azetidinones are potent elastase inhibitors and therefore are useful anti-inflammatory/antidegenerative agents.

5 Proteases from granulocytes and macrophages have been reported to be responsible for the chronic tissue destruction mechanisms associated with inflammation, including rheumatoid arthritis and emphysema. Accordingly, specific and selective inhibitors of these proteases are candidates for potent anti-inflammatory agents useful in the treatment of inflammatory conditions resulting in connective tissue destruction, e.g. rheumatoid arthritis, emphysema, bronchial inflammation, osteoarthritis, spondylitis, lupus.  
 10 psoriasis, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis and acute respiratory distress syndrome.

The role of proteases from granulocytes, leukocytes or macrophages are related to a rapid series of events which occurs during the progression of an inflammatory condition:

(1) There is a rapid production of prostaglandins (PG) and related compounds synthesized from arachidonic acid. This PG synthesis has been shown to be inhibited by aspirin-related nonsteroidal anti-inflammatory agents including indomethacin and phenylbutazone. There is some evidence that protease inhibitors prevent PG production;

(2) There is also a change in vascular permeability which causes a leakage of fluid into the inflamed site and the resulting edema is generally used as a marker for measuring the degree of inflammation. This process has been found to be induced by the proteolytic or peptide cleaving activity of proteases, especially those contained in the granulocyte, and thereby can be inhibited by various synthetic protease inhibitors, for example, N-acyl benzothiazolones and the respective 1,1-dioxides. Morris Zimmerman et al., J. Biol. Chem., 255, 9848 (1980); and

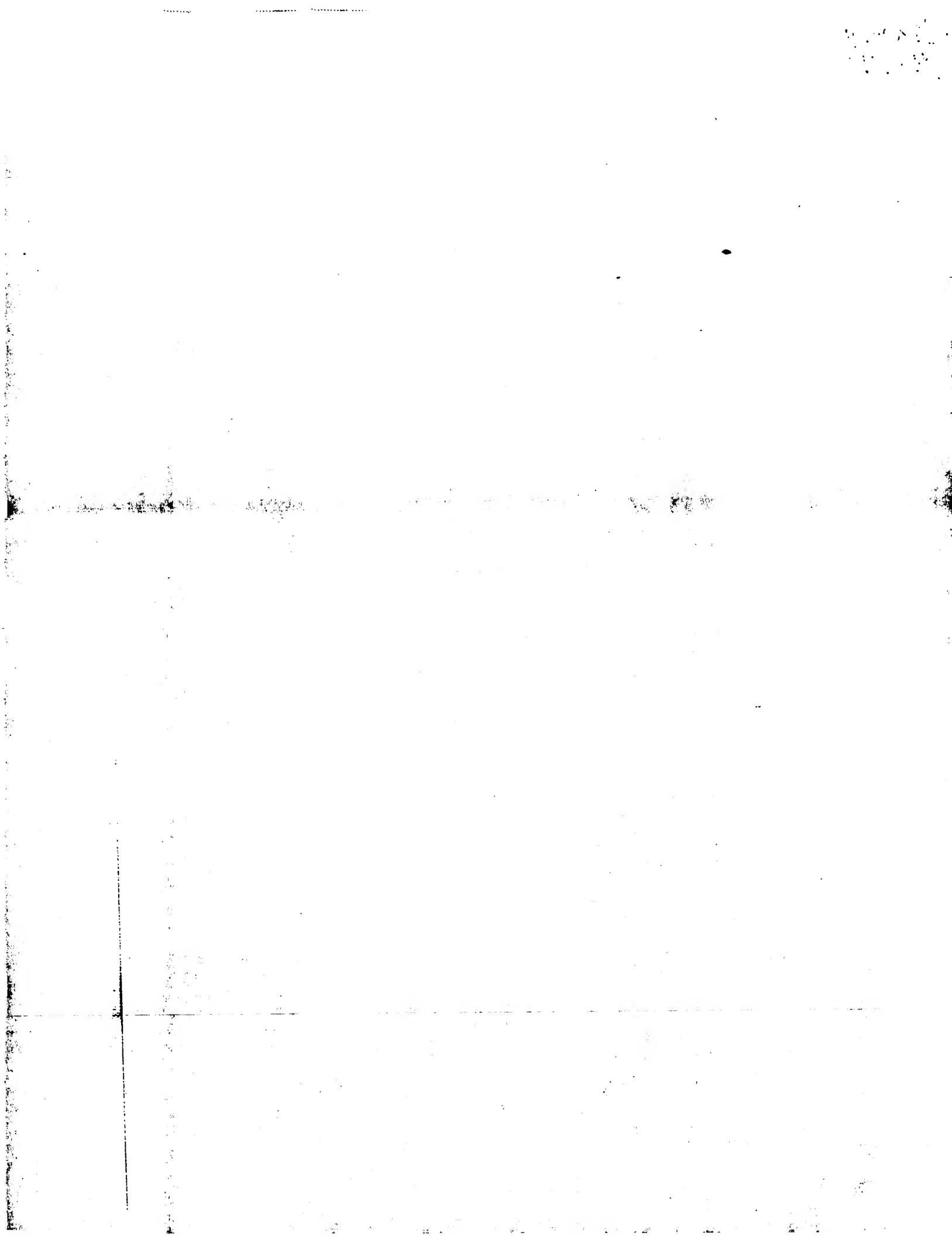
(3) There is an appearance and/or presence of lymphoid cells, especially macrophages and polymorphonuclear leukocytes (PMN). It has been known that a variety of proteases are released from the macrophages and PMN, further indicating that the proteases do play an important role in inflammation.

In general, proteases are an important family of enzymes within the peptide bond cleaving enzymes whose members are essential to a variety of normal biological activities, such as digestion, formation and dissolution of blood clots, the formation of active forms of hormones, the immune reaction to foreign cells and organisms, etc., and in pathological conditions such as the degradation of structural proteins at the articular cartilage:pannus junction in rheumatoid arthritis etc.

Elastase is one of the proteases. It is an enzyme capable of hydrolyzing the connective tissue component elastin, a property not contained by the bulk of the proteases present in mammals. It acts on a protein's nonterminal bonds which are adjacent to an aliphatic amino acid. Neutrophil elastase is of particular interest because it has the broadest spectrum of activity against natural connective tissue substrates. In particular, the elastase of the granulocyte is important because, as described above, granulocytes participate in acute inflammation and in acute exacerbation of chronic forms of inflammation which characterize many clinically important inflammatory diseases.

40 Proteases may be inactivated by inhibitors which block the active site of the enzyme by binding tightly thereto. Naturally occurring protease inhibitors form part of the control or defense mechanisms that are crucial to the well-being of an organism. Without these control mechanisms, the proteases would destroy any protein within reach. The naturally occurring enzyme inhibitors have been shown to have appropriate configurations which allow them to bind tightly to the enzyme. This configuration is part of the reason that 45 inhibitors bind to the enzyme so tightly (see Stroud, "A Family of Protein-Cutting Proteins" Sci. Am. July 1974, pp. 74-88). For example, one of the natural inhibitors,  $\alpha_1$ -Antitrypsin, is a glycoprotein contained in human serum that has a wide inhibitory spectrum covering, among other enzymes, elastase both from the pancreas and the PMN. This inhibitor is hydrolyzed by the proteases to form a stable acyl enzyme in which the active site is no longer available. Marked reduction in serum  $\alpha_1$ -antitrypsin, either genetic or due to 50 oxidants, has been associated with pulmonary emphysema which is a disease characterized by a progressive loss of lung elasticity and resulting respiratory difficulty. It has been reported that this loss of lung elasticity is caused by the progressive, uncontrolled proteolysis or destruction of the structure of lung tissue by proteases such as elastase released from leukocytes. J. C. Powers, TIBS, 211 (1976).

Rheumatoid arthritis is characterized by a progressive destruction of articular cartilage both on the free



surface bordering the joint space and at the erosion front built up by synovial tissue toward the cartilage. This destruction process, in turn, is attributed to the protein-cutting enzyme elastase which is a neutral protease present in human granulocytes. This conclusion has been supported by the following observations:

5 (1) Recent histochemical investigations showed the accumulation of granulocytes at the cartilage/pannus junction in rheumatoid arthritis; and

(2) a recent investigation of mechanical behavior of cartilage in response to attack by purified elastase demonstrated the direct participation of granulocyte enzymes, especially elastase, in rheumatoid cartilage destruction. H. Menninger et al., in Biological Functions of Proteinases, H. Holzer and H. Tschesche, eds. Springer-Verlag, Berlin, Heidelberg, New York, pp. 196-206, 1979.

10 Accordingly, an object of this invention is to discover new protease inhibitors, especially elastase inhibitors, useful for controlling tissue damage and various inflammatory or degenerative conditions mediated by proteases particularly elastase.

15 Another object of the present invention is to provide pharmaceutical compositions for administering the active substituted azetidinones as protease inhibitors especially human leukocyte elastase.

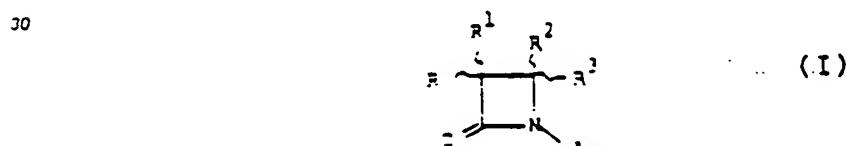
Still a further object of this invention is to provide a method of controlling inflammatory conditions by administering a sufficient amount of one or more of the active, substituted azetidinones in a mammalian species in need of such treatment.

20 DETAILED DESCRIPTION OF THE INVENTION

This invention relates to potent elastase inhibitors of formula (I) which are useful in the prevention, control and treatment of inflammatory/degenerative conditions especially arthritis and emphysema.

25 A large number of the azetidinone derivatives of formula (I) are known antibiotics which have been described in patents and various publications.

The formula of the substituted azetidinones which are found to exhibit anti-inflammatory and antidegenerative activities by the present invention are represented as follows:



35

wherein

R can be at the  $\alpha$  or the  $\beta$ -position and is hydrogen, straight or branched loweralkyl especially C<sub>1</sub>-<sub>6</sub>alkyl, such as methyl, ethyl, n- or i-propyl, butyl, pentyl or hexyl; or loweralkyl substituted with a radical

40 R<sup>4</sup> as defined below; or halo such as fluoro, chloro or bromo;

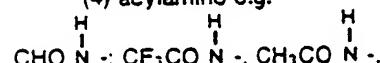
R<sup>1</sup> can be at the  $\alpha$ - or the  $\beta$ -position and is

(1) OB or -S(O)<sub>n</sub>B wherein B is as defined below and n is 0, 1 or 2;

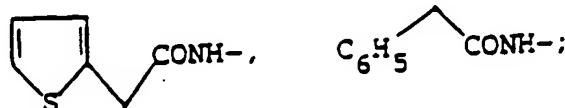
(2) Straight or branched loweralkenyl especially C<sub>2</sub>-<sub>6</sub>alkenyl such as vinyl, allyl, -CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>, and -CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>;

45 (3) loweralkyl as defined above;

(4) acylamino e.g.



50



55

or

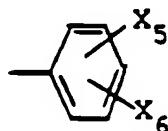
(5) amino:

(6) Straight or branched loweralkynyl group especially C<sub>3</sub>-alkynyl such as -C≡CH, -CH<sub>2</sub>-C≡CH and -CH<sub>2</sub>CH<sub>2</sub>-C≡CCH<sub>3</sub>;

(7) An aryl group having 6-14 carbon atoms as described below such as phenyl of formula

5

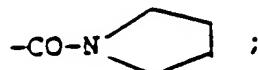
10



wherein X<sub>5</sub> and X<sub>6</sub> independently are:

- 1) Q, where Q is H, loweralkyl, haloloweralkyl, phenyl or substituted phenyl as previously defined, or naphthyl;
- 15 2) halo;
- 3) loweralkenyl;
- 4) loweralkynyl;
- 5) -SQ;
- 6) -OQ;
- 20 7) -CHQCQ<sup>1</sup>, where Q<sup>1</sup> is defined as Q and Q<sup>1</sup> can be the same as or different from Q;
- 8) -CHQCQQ<sup>1</sup> such as CH<sub>2</sub>COOH;
- 9) -CH<sub>2</sub>SQ;
- 10) -CHQSQ<sup>1</sup>;
- 11) -CH<sub>2</sub>OQ or -CHQOQ<sup>1</sup> especially -CH<sub>2</sub>OH and -CH<sub>2</sub>OCH<sub>3</sub>;
- 25 12) -COQ for example, -COCH<sub>3</sub> and -(CO)H;
- 13) -COOQ especially -COOH and COOt-Bu;
- 14) -OCOOQ such as -OCOCH<sub>3</sub>;
- 15) -NQQ<sup>1</sup>;
- 16) -NQCOQ<sup>1</sup> especially -NHCOCH<sub>3</sub>;
- 30 17) -CH<sub>2</sub>NH<sub>2</sub> or -CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>I<sup>-</sup>;
- 18) -CH<sub>2</sub>OCOCH<sub>3</sub>;
- 19) -NQSO<sub>2</sub>Q<sup>1</sup>;
- 20) -SO<sub>2</sub>NQQ<sup>1</sup>;
- 21) -SOQ;
- 35 22) -SO<sub>2</sub>Q;
- 23) -SO<sub>3</sub>Q;
- 24) -CN;
- 25) -NO<sub>2</sub>;
- 26) -CONQQ<sup>1</sup>;
- 40 27) -NO;
- 28) -CSQ;
- 29) -CSNQQ<sup>1</sup>;
- 30) -CF<sub>2</sub>SQ;
- 31) -CF<sub>2</sub>OQ;
- 45 32) -NQCONHQ<sup>1</sup> or NQCONQ<sup>1</sup>Q<sup>2</sup> where Q<sup>2</sup> is defined as Q<sup>1</sup> and Q<sup>2</sup> can be the same as or different from Q<sup>1</sup>;
- 33) -CH<sub>2</sub>Y wherein Y represents -CH(NHAC)COO<sup>-</sup>, CH(NH<sub>3</sub>)<sub>2</sub>COO<sup>-</sup>, CH<sub>2</sub>COOH, COOH, -N(CH<sub>3</sub>)<sub>2</sub>, OH, CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, or CH<sub>2</sub>OH;
- 34) -CH(C<sub>1</sub>-alkyl);
- 50 35) -NH(CO)CH<sub>2</sub>CH<sub>2</sub>COOH;
- 36)

55

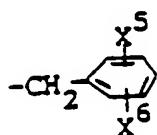


or

37) -CO-NH-SO<sub>2</sub>phenyl or substituted phenyl such as p-chlorophenyl;

8) heteroaryl such as unsubstituted or substituted furyl, thienyl, thiazolyl, pyrrolyl, pyrimidinyl, pyridyl, oxazolyl, tetrazolyl or imidazolyl wherein the substituents are as those described for substituted phenyls;  
 9) aralkyl especially phenyl  $C_1$ -alkyl such as benzyl of formula

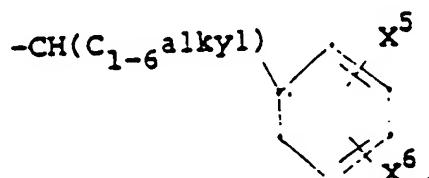
5



10

or

15



20

or phenethyl:

(10) halo such as F, Cl, Br or I;

(11) N<sub>3</sub>;

(12) hydrogen;

25 (13) R and R' may join together and form a cycloalkyl such as a  $C_1$ -cycloalkyl, e.g., cyclopentan = C(B)(B<sub>1</sub>) or = O (oxo) wherein B and B<sub>1</sub> independently are as defined below;(14) -CH<sub>2</sub>OC<sub>1</sub>-alkyl especially -CH<sub>2</sub>OCH<sub>3</sub> and -CH<sub>2</sub>OC<sub>2</sub>H<sub>5</sub>;(15) -CH<sub>2</sub>CH<sub>2</sub>OC<sub>1</sub>-alkyl especially -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>H<sub>5</sub>;30 R<sup>2</sup> and R<sup>3</sup> can be at the  $\alpha$  or the  $\beta$ -position and independently are

(1) B as defined below;

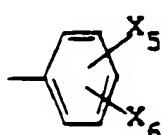
(2) -CONBB' wherein B and B' independently represent

(a) H;

(b) straight or branched alkyl having from 1 to 20 carbon atoms, preferably  $C_1$ -alkyl such as methyl, ethyl, isopropyl, t-butyl, pentyl or hexyl;

35 (c) aryl having from 6 to 14 carbon atoms such as phenyl or substituted phenyl of formula

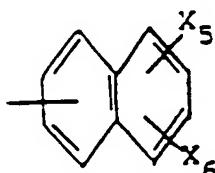
40



45

naphthyl or substituted naphthyl of formula

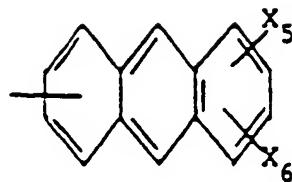
50



55

or anthracenyl or substituted anthracenyl of formula

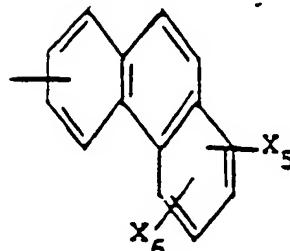
5



10

or

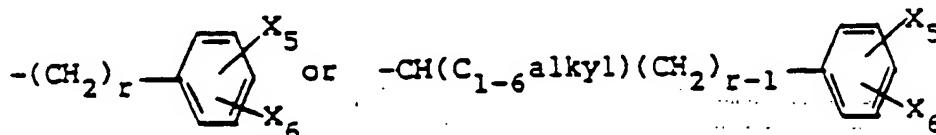
15



20

- (d) cycloalkyl having from 3 to 8 carbon atoms especially cyclopropyl, cyclopentyl or cyclohexyl;  
 (e) straight or branched alkenyl having from 2 to 20 carbon atoms, for example, allyl;  
 (f) straight or branched alkynyl having from 2 to 20 carbon atoms, for example,  $\text{C}\equiv\text{CH}$ ;  
 (g) aralkyl, alkaryl, aralkenyl, aralkynyl, alkenylaryl or  
 25 alkynylaryl wherein alkyl, aryl, alkenyl and alkynyl are as previously defined for example,  $\text{C}_1\text{-6}$  alkylphenyl of formula

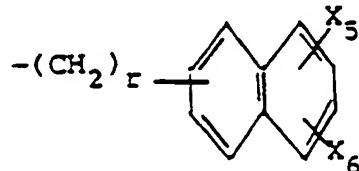
30



35

wherein r is 1 to 6,  $\text{C}_1\text{-6}$  alkyl naphthyl of formula

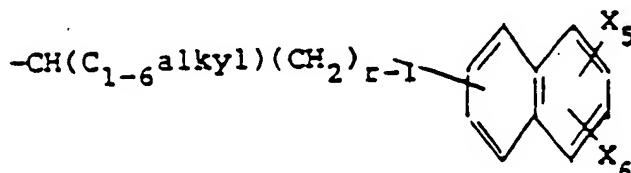
40



45

or

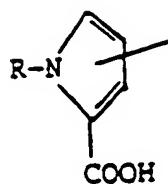
50



55

- (h) heteroaryl comprising monoheteroaryl, di- or polyheteroaryl, or fused heteroaryl containing from 1 to 3 of any one or more of the heteroatoms N, S or O in each heteroaryl ring thereof, for example, pyndyl, pyrryl, such as

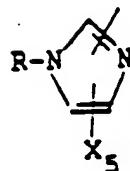
5



10

thienyl, isothiazolyl, imidazolyl such as

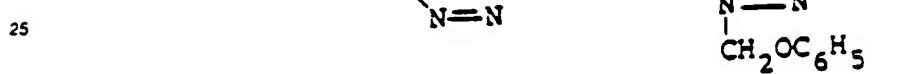
15



20

tetrazolyl such as

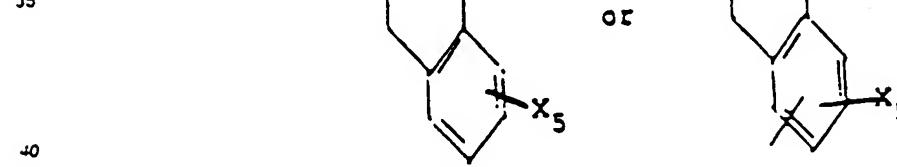
25



30

pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl such as

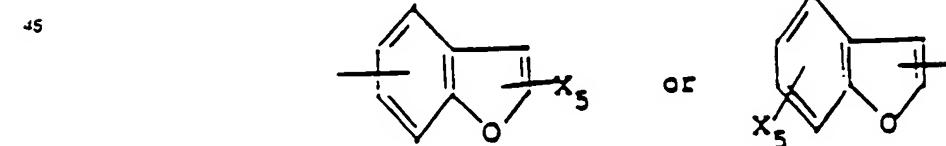
40



50

benzothienyl, benzofuryl such as

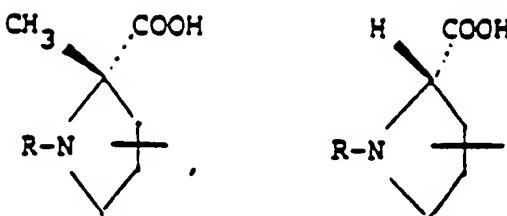
45



55

pyrazolyl, indolyl, purinyl, carbazolyl, isoxazolyl and the like:

(i) heteroarylalkyl such as 2-pyridylmethyl, 2-thienylmethyl and 3-isothiazolylethyl; or  
(j) heterocycloalkyl e.g., 1,3-dioxacyclohex-4-yl, piperidino.

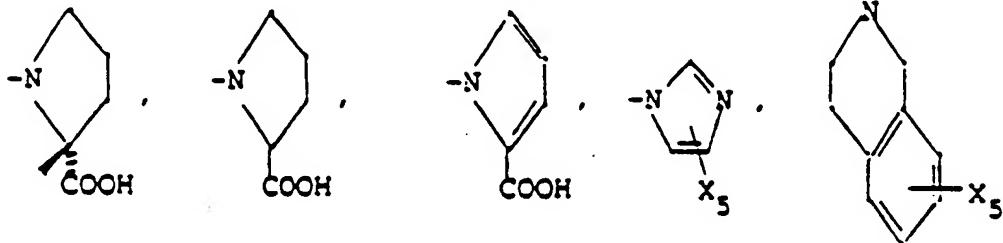


- 10 morpholino, oxacyclopropyl, pyrrolidino, benzothiazolino, imidazolidino, pyrazolidino, and piperazino;  
 (k) heterocycloalkenyl such as pyrrolino, 2-imidazolino, 3-pyrazolino or isoindolino;  
 (l) B and B<sub>1</sub> joined together and form a heterocyclic ring containing at least one N-atom and optionally 1 to 3 of the heteroatoms, N, S, or O, e.g.,

15

20

25



- the above groups (a)-(l) can be unsubstituted or can be substituted by one or more radical R<sup>4</sup> selected from the group consisting of loweralkyl, hydroxy, aryloxy (OAr), alkoxy, halo, nitro, loweralkylthio, arylthio, mercapto, amino, monoalkyl or dialkyl substituted amino, cyano, carboxy, loweralkanoyl, Ar(C=O), aminosulfonyl, aminosulfenyl, aminosulfinyl, carbamoyl, carbamoyloxy, -S(O)<sub>n</sub>R<sup>5</sup>, SO<sub>3</sub>R<sup>5</sup>, -P(O)<sub>q</sub>R<sup>5</sup> (where q is 1 or 2 and R<sup>5</sup> is H, C<sub>1</sub>-<sub>6</sub> alkyl, aralkyl or aryl as previously defined), azido, carboxamido or N-substituted carboxamido:

- (3) -S(O)<sub>n</sub>B;  
 (4) -S(O)<sub>n</sub>NBB<sub>1</sub>;  
 (5) -N(B)S(O)<sub>n</sub>B<sub>1</sub>;  
 (6) -P(O)<sub>q</sub>BB<sub>1</sub>;  
 (7) -C(O)B especially acetyl, benzoyl, e.g., p-chlorobenzoyl, p-methylbenzoyl and p-aminosulfonylbenzoyl;  
 (8) -OB especially -OC<sub>1</sub>-<sub>6</sub>alkyl, phenoxy or substituted phenoxy of formula

45



- (9) -COOB, -OC(O)OB or OC(O)NBB<sub>1</sub>;  
 (10) -O-C(O)-B especially C<sub>1</sub>-<sub>6</sub>alkanoyloxy such as acetoxy;  
 (11) cyano;  
 (12) -S-C(O)-B especially C<sub>1</sub>-<sub>6</sub>alkanylthio such as acetylthio; or  
 (13) R<sup>2</sup> and R<sup>3</sup> may join and form =C(B<sub>1</sub>)(B), a C<sub>1</sub>-cycloalkyl for example, cyclopentyl, and =O-(OXO);
- 55 A is  
 (1) -O-C(O)-B;  
 (2) -S(O)<sub>n</sub>B;  
 (3) -S(O)<sub>n</sub>NBB<sub>1</sub>;

(4) -C(O)B:

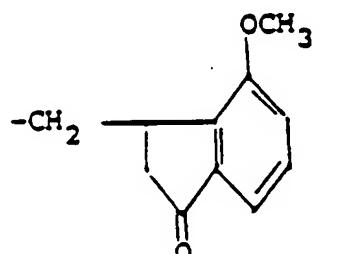
(5) SO<sub>3</sub>-M where M represents(a) an alkali anion such as Na<sup>-</sup>, K<sup>-</sup>; or(b) a quaternary ammonium group of formula N<sup>+</sup>(R<sup>5</sup>)<sub>4</sub>, for example, (n-Bu)<sub>4</sub>N<sup>+</sup>:5 (6) substituted or unsubstituted phosphoryl or phosphonyl such as -P(O)<sub>3</sub>(R<sup>5</sup>)<sub>2</sub> or -P(O)<sub>2</sub>R<sup>5</sup>:(7) -C(O)NBB<sub>1</sub>, especially -CON(C<sub>2</sub>H<sub>5</sub>)Phenyl and -CONHBB<sub>1</sub>, wherein B<sub>1</sub> is(a) -(CH<sub>2</sub>)<sub>n</sub>Ph, or CH(C<sub>1</sub>-<sub>6</sub>alkyl)(CH<sub>2</sub>)<sub>n</sub>Ph, e.g., -CH(C<sub>2</sub>H<sub>5</sub>)Ph, -CH(C<sub>3</sub>H<sub>7</sub>)Ph, -CH-(allyl)-Ph, -CH(C<sub>2</sub>H<sub>5</sub>)CH<sub>2</sub>Ph, or -CH(CH<sub>3</sub>)<sub>2</sub>Ph wherein Ph represents phenyl or substituted phenyl as previously defined, for examples, 4-methyl-phenyl, 4-methoxyphenyl, 4-N,N-dimethyl-amino-phenyl, 4-benzyloxy-phenyl, 4-phenyl-

10 phenyl, 3,4-methylenedioxy-phenyl, and 3,4-dimethyl-phenyl;

(b) -(CH<sub>2</sub>)<sub>n</sub>(Naph) especially -CH<sub>2</sub>(Naph) or -CH(C<sub>2</sub>H<sub>5</sub>)(Naph) wherein (Naph) is  $\alpha$  or  $\beta$ -naphthyl or substituted naphthyl as previously defined;(c) -(CH<sub>2</sub>)<sub>n</sub>(Ar) especially -CH<sub>2</sub>CH<sub>2</sub>Ar or -CH<sub>2</sub>Ar wherein Ar represents heteroaryl especially 2-thienyl, 2-furyl, 3-thienyl, or benzofuryl;15 (d) -(CH<sub>2</sub>)<sub>n</sub>OPh especially -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OPh;(e) -(CH<sub>2</sub>)<sub>n</sub>CH(OH)Ph;(f) -(CH<sub>2</sub>)<sub>n</sub>(CO)Ph;

(g)

20



25

30 (h)

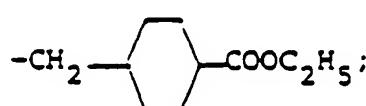


35

(i) -CH<sub>2</sub>-Ph(p-CO-NH-SO<sub>2</sub>-Ph(p-Cl)):

(j)

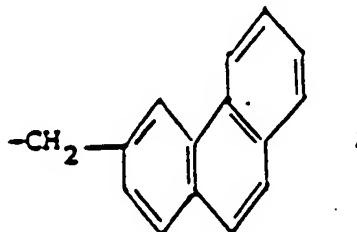
40



45

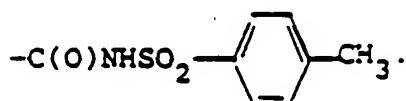
(k)

50



55

or

(I) -CH(CH<sub>3</sub>)-Ph(p-cyclohexyl);(8) -C(O)OB especially C: -s alkoxycarbonyl, e.g., methoxycarbonyl, and -ethoxycarbonyl or C OOCH<sub>2</sub>-Ph(p-COOC<sub>2</sub>H<sub>5</sub>);(9) halo C<sub>1</sub>-s alkyl such as trifluoromethyl;5 (10) -OB especially -O-CH<sub>2</sub>-(phenyl or substituted phenyl as previously defined), for example, -OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>; -OCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-OCH<sub>3</sub>; or OCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>;(11) silyl such as -Si(CH<sub>3</sub>)<sub>2</sub>(t-Bu);10 R<sup>s</sup> is as previously defined and L is a good leaving group comprising OAc, SAC, halogen, OR<sup>s</sup>, SR<sup>s</sup>, SOR<sup>s</sup>, SO<sub>2</sub>R<sup>s</sup>, OTs, OCOCF<sub>3</sub>, and mesyl wherein Ac is acetyl; and Ts is tosyl; or  
(13)

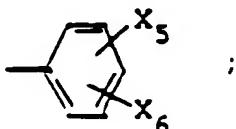
Preferably, the compounds of the present invention are of formula (I) wherein:

20 R is hydrogen; or C<sub>1</sub>-s alkyl;R<sup>t</sup> is(1) C<sub>1</sub>-s alkyl especially methyl or ethyl(2) OR<sup>s</sup>:

(3) phenyl of formula

25

30

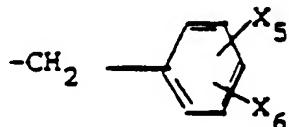


(4) hydrogen;

(5) benzyl of formula

35

40

45 (6) CH<sub>2</sub>OC<sub>1</sub>-s alkyl or -CH<sub>2</sub>CH<sub>2</sub>OC<sub>1</sub>-s alkyl;(7) C<sub>2</sub>-s alkenyl; or(8) R and R<sup>t</sup> may join together and form a cyclopentane;R<sup>2</sup> and R<sup>3</sup> independently are

(1) hydrogen;

(2) S(O)<sub>n</sub>R<sup>s</sup>;

(3) COOB;

50 (4) CONBB<sub>1</sub>;

(5) OB;

(6) C<sub>1</sub>-s alkyl;

(7) phenyl or substituted phenyl as previously defined;

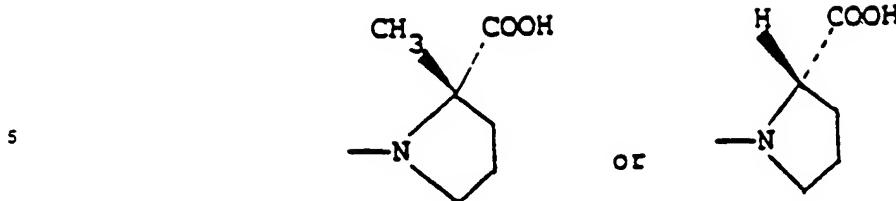
(8) naphthyl as previously defined;

55 (9) cyclohexyl;

(10) benzyl as previously defined;

(11) heteroaryl selected from a group consisting of imidazolyl, benzofuryl and tetrahydroisoquinolyl;

(12) heterocycloalkyl such as

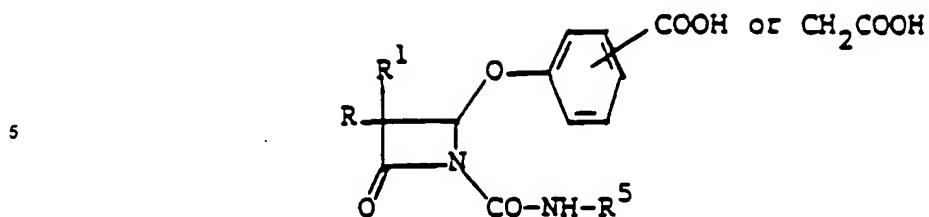


- 10      A      (13) C(O)B;  
       is  
       (1) SOR<sup>5</sup>;  
       (2) SO<sub>2</sub>R<sup>5</sup>;  
       (3) COOB;  
       (4) C(O)B;  
       (5) CONBB<sub>1</sub> wherein B and B<sub>1</sub> independently are:  
           (a) H;  
           (b) C<sub>1</sub>-<sub>5</sub>alkyl;  
           (c) -(CH<sub>2</sub>)<sub>r</sub>Ph where r represents 1 or 2 and Ph represents phenyl or substituted phenyl as previously defined;  
           (d) CH(C<sub>1</sub>-<sub>5</sub>alkyl)(CH<sub>2</sub>)<sub>r</sub>Ph where Ph is as defined above;  
           (e) phenyl or substituted phenyl as previously defined such as p-methoxyphenyl, p-nitrophenyl and p-methylphenyl;  
           (f) C<sub>1</sub>-<sub>5</sub> alkyl;  
           (g) CH<sub>2</sub>OH;  
           (h) CH<sub>2</sub>OC(O)CH<sub>3</sub>; or  
           (i) -C(O)NHSO<sub>2</sub>-Ph(p-CH<sub>3</sub>).

Even more preferably, the compounds of the present invention are of formula (I) wherein

- 30      R      is hydrogen or C<sub>1</sub>-<sub>3</sub>alkyl;  
     R'      is  
           (1) hydrogen;  
           (2) C<sub>1</sub>-<sub>5</sub>alkyl;  
           (3) C<sub>1</sub>-<sub>5</sub>alkoxy such as methoxy;  
           (4) C<sub>2</sub>-<sub>5</sub>alkenyl;  
           (5) phenyl or substituted phenyl as previously defined; or  
           (6) CH<sub>2</sub>OC<sub>1</sub>-<sub>3</sub> alkyl;  
     R<sup>2</sup>      is hydrogen;  
     R<sup>3</sup>      is  
           (1) S(O)<sub>n</sub>R<sup>5</sup>;  
           (2) CONBB<sub>1</sub>;  
           (3) COOB;  
           (4) phenoxy or substituted phenoxy;  
           (5) imidazolyl; or  
           (6) substituted or unsubstituted alkoxy, for example, OCH<sub>3</sub> or -OCH<sub>2</sub>CONH<sub>2</sub>;  
         45      A      is  
           (1) CO<sub>2</sub>R<sup>5</sup> wherein R<sup>5</sup> is H, C<sub>1</sub>-<sub>5</sub> alkyl, -CH<sub>2</sub>Ph, -CH(CH<sub>3</sub>)Ph, -CH(C<sub>2</sub>H<sub>5</sub>)Ph, CH(C<sub>3</sub>H<sub>7</sub>)Ph or CH-(C<sub>3</sub>H<sub>5</sub>)Ph wherein Ph represents phenyl or substituted phenyl as previously defined;  
           (2) CONHR<sup>5</sup>; or  
           (3) SO<sub>2</sub>R<sup>5</sup>.

The most preferred compounds of the present invention are listed in the following table.



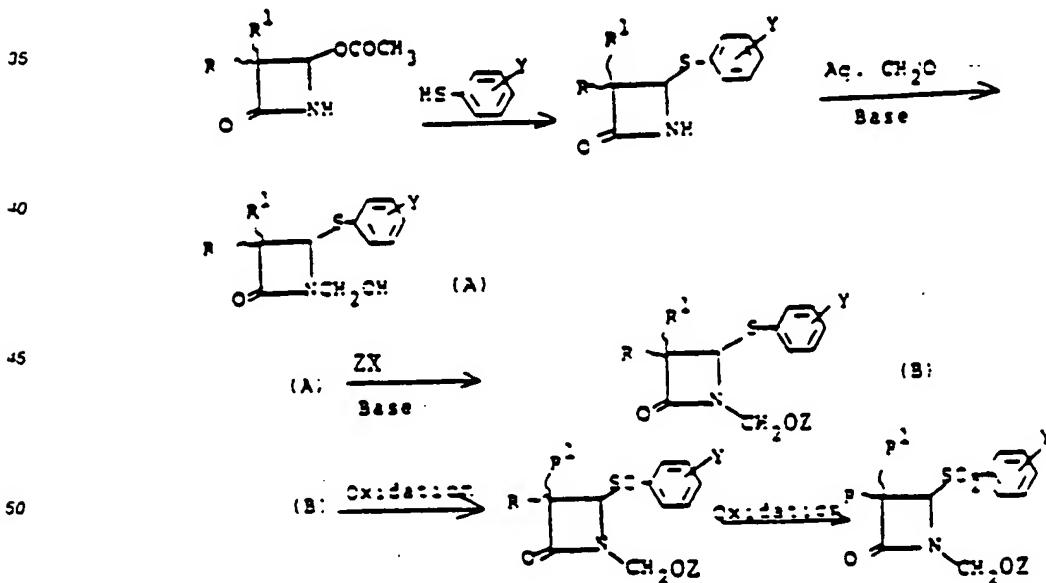
	R	R'	R<sup>5</sup>
15	C<sub>2</sub>H<sub>5</sub>	CH<sub>3</sub>	CH(CH<sub>3</sub>)Ph
	C<sub>2</sub>H<sub>5</sub>	C<sub>2</sub>H<sub>5</sub>	CH<sub>2</sub>-(4-Ph-Ph)
	C<sub>2</sub>H<sub>5</sub>	CH<sub>3</sub>	CH(C<sub>2</sub>H<sub>5</sub>)Ph
	C<sub>2</sub>H<sub>5</sub>	C<sub>2</sub>H<sub>5</sub>	CH(C<sub>2</sub>H<sub>5</sub>)Ph
	C<sub>2</sub>H<sub>5</sub>	CH<sub>2</sub>OCH<sub>3</sub>	CH(C<sub>2</sub>H<sub>5</sub>)Ph
20	C<sub>2</sub>H<sub>5</sub>	C<sub>2</sub>H<sub>5</sub>	CH(C<sub>3</sub>H<sub>7</sub>)-(4-CH<sub>3</sub>-Ph)
	C<sub>2</sub>H<sub>5</sub>	C<sub>2</sub>H<sub>5</sub>	CH(C<sub>3</sub>H<sub>5</sub>)-(4-CH<sub>3</sub>-Ph)
	C<sub>2</sub>H<sub>5</sub>	C<sub>2</sub>H<sub>5</sub>	CH(C<sub>3</sub>H<sub>7</sub>)Ph
	C<sub>2</sub>H<sub>5</sub>	C<sub>2</sub>H<sub>5</sub>	CH(C<sub>3</sub>H<sub>7</sub>)-(3,4-methylenedioxy-Ph)
	C<sub>2</sub>H<sub>5</sub>	C<sub>2</sub>H<sub>5</sub>	CH(C<sub>3</sub>H<sub>5</sub>)-(3,4-methylenedioxy-Ph)

25 In the above table, Ph represents phenyl or substituted phenyl as previously defined.

The compounds of the present invention are either known or are prepared among other methods by the following representative schemes.

30 Scheme (a)

as illustrated by Examples 16-19.



55 wherein

Y is -NO<sub>2</sub>, -CH<sub>3</sub>, -OCH<sub>3</sub>, -Cl, -F, etc;

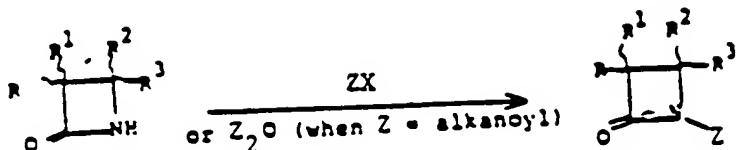
X is halo, e.g., Cl, Br or I;

Z is BCO or BSO<sub>2</sub>.

Scheme (b)

as illustrated by Examples 1-4.

5



10

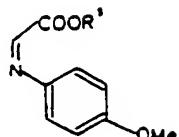
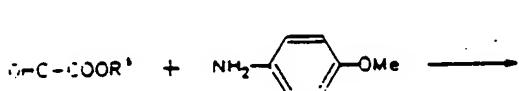
wherein

X is halo;

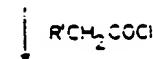
Z is as previously defined, e.g.,  $-\text{SO}_2-(p\text{-NO}_2\text{-Ph})$ ,  $-\text{COCH}_3$ ,  $-\text{CH}_2\text{OTs}$ , etc. wherein Ph represents phenyl or  
15 substituted phenyl.Scheme(c)

as illustrated by Examples 5-15

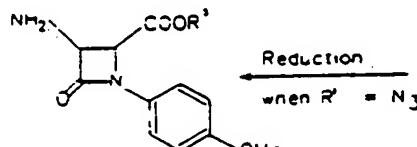
20



25



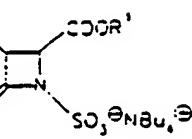
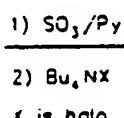
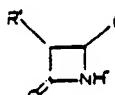
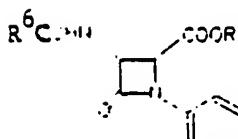
30



35

activation  
 $\text{R}'\text{COX}$

CAN



45

wherein

 $\text{R}^6$  is  $\text{H}$ ,  $\text{CF}_3$ ,  $\text{CH}_3$ , etc.; $\text{R}^3$  and  $\text{R}'$  are as previously defined; and

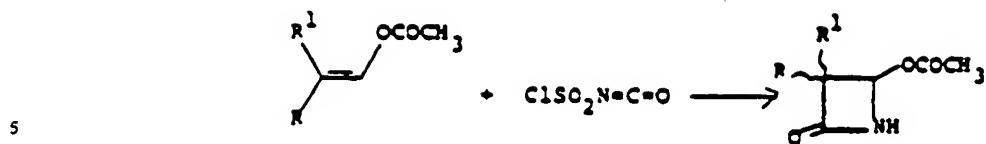
CAN is ceric ammonium nitrate.

50

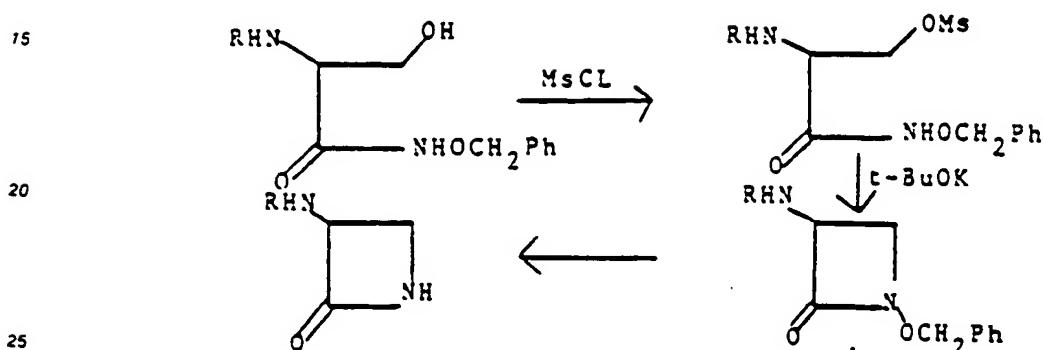
Scheme (d)

as illustrated by Examples 2-3.

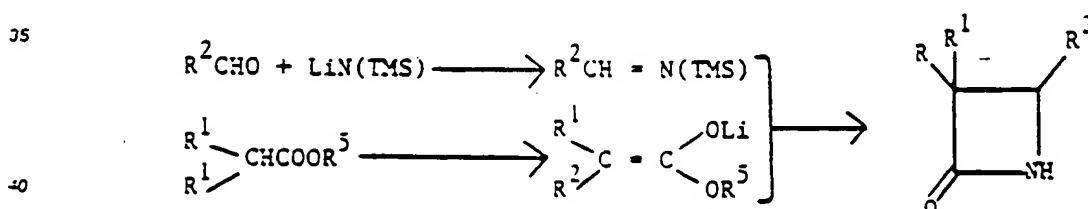
55

Scheme (e)

10 as taught by M. A. Krook and M. J. Miller (J. Org. Chem., 1985, 50, 1126-1128), the following type of compounds can be prepared.

Scheme (f)

30 as taught by Hart, D. J. et al. (J. Org. Chem., 48, pp. 289-294, 1983); the following class of compounds can be prepared.



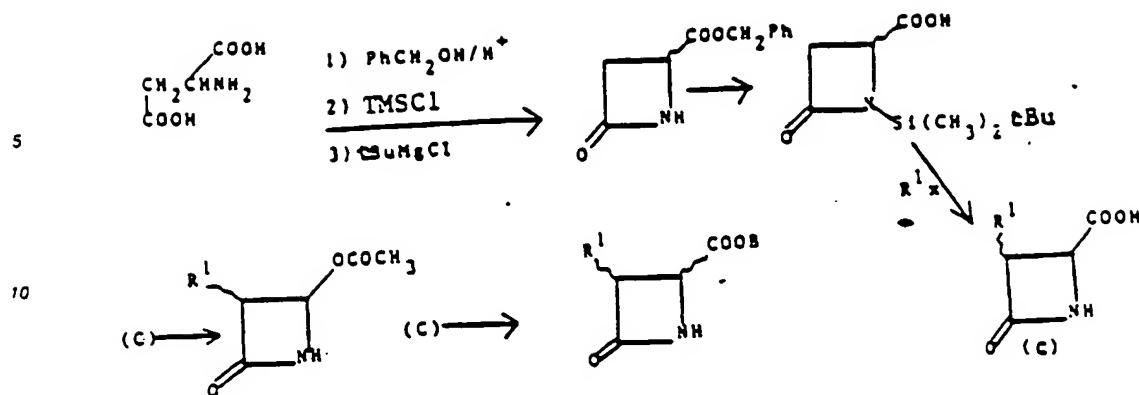
wherein  $\text{R}^5$  is as previously defined; and  
TMS is trimethylsilyl.

Scheme (g)

45 as taught by P. J. Reider and E. J. J. Grabowski (Tet. Lett., 23, p. 2293, 1982); the following groups of compounds can be prepared.

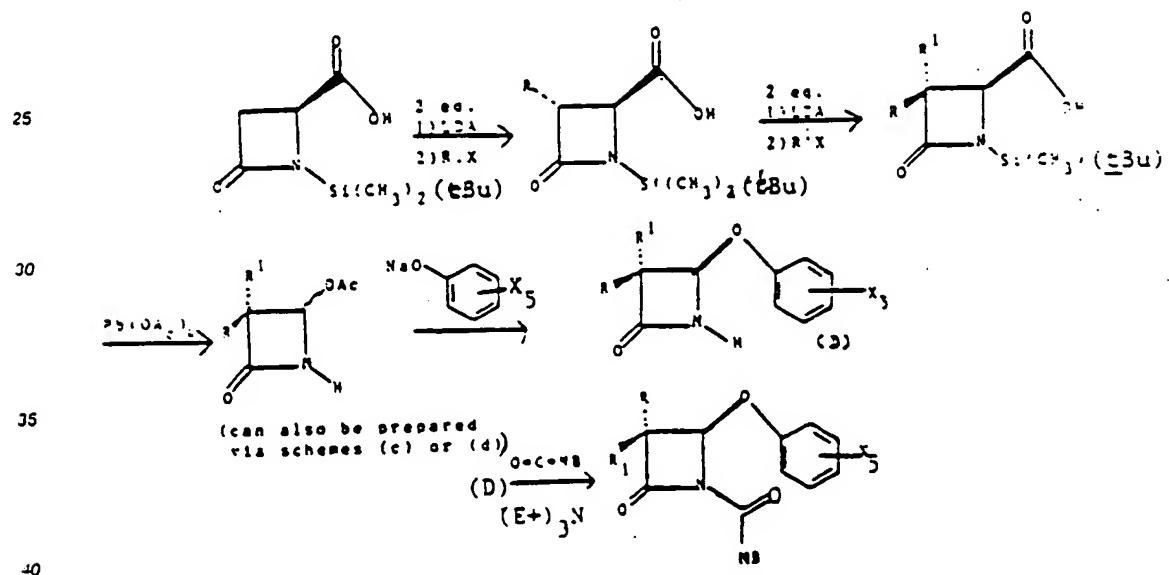
50

55



Scheme (h)

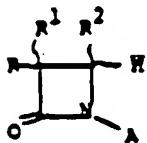
20 as illustrated by Examples 20 and 21:



This invention also relates to a method of treating inflammation in patients using a compound of Formula (I), particularly a preferred compound as the active constituent.

45 It has been found that the compounds of Formula (I) are effective inhibitors of the proteolytic function of human granulocyte elastase as shown below:

TABLE I



10

10

	R	R¹	R²	A	I <sub>D<sub>50</sub></sub> (µg/ml)	K <sub>i</sub> (µM)	k <sub>obs</sub> /I (M <sup>-1</sup> sec <sup>-1</sup> )
20	H	H	SOCH <sub>3</sub>	COCH <sub>3</sub>	10.00		
	H	H	OOCCH <sub>3</sub>	COCH <sub>3</sub>	3.00		
	H	C <sub>2</sub> H <sub>5</sub>	OOCCH <sub>3</sub>	H	15.00		
	H	C <sub>2</sub> H <sub>5</sub>	OOCCH <sub>3</sub>	COCH <sub>3</sub>	0.10	0.36	15100
25	H	n-propyl	OOCCH <sub>3</sub>	COCH <sub>3</sub>	0.01		
	H	C <sub>6</sub> H <sub>5</sub> (trans)	COOC <sub>2</sub> H <sub>5</sub>	H	10.00		
	H	H	COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	3.00		
	CH <sub>3</sub>	CH <sub>3</sub>	OOCCH <sub>3</sub>	COCH <sub>3</sub>	0.50		
30	H	C <sub>6</sub> H <sub>5</sub> (trans)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	4.00		
	H	C <sub>6</sub> H <sub>5</sub> (cis)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	3.00		
	H	CH <sub>3</sub> O	COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	COCH <sub>3</sub>	2.00		
	H	n-propyl	OOCCH <sub>3</sub>	SO <sub>3</sub> <sup>-</sup> (Bu) <sub>4</sub> N <sup>+</sup>	8.00		
35	H	C <sub>2</sub> H <sub>3</sub> (cis)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	0.02		
	H	C <sub>2</sub> H <sub>5</sub> (cis)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	0.05	3925	
	H	C <sub>2</sub> H <sub>5</sub> (trans)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	0.05		19300
	H	C <sub>2</sub> H <sub>5</sub> (trans)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> )	0.01		
40	H	n-propyl (trans)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	0.06		
	H	CH <sub>3</sub> CHCH (cis)	COOC <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	0.05		
	H	CH <sub>2</sub> CH	p-(C <sub>6</sub> H <sub>4</sub> -NO <sub>2</sub> )	H	1.50		
	H	C <sub>2</sub> H <sub>5</sub>	OOCCH <sub>2</sub> CH <sub>2</sub> COOH	COCH <sub>3</sub>	2.00	4514	
50	H	C <sub>2</sub> H <sub>5</sub> (trans)	OCOPh	COCH <sub>3</sub>	0.19	91000	

TABLE I (Continued)

S	R	R <sup>1</sup>	R <sup>2</sup>	A	ID <sub>50</sub> (μg/ml)	Ki (μM)	k <sub>obs</sub> /I (M <sup>-1</sup> sec <sup>-1</sup> )
10	H	C <sub>2</sub> H <sub>5</sub> (cis)	OCOPh	COCH <sub>3</sub>	0.21	28500	
	H	C <sub>2</sub> H <sub>5</sub>	OCOCH <sub>3</sub>	COCH <sub>2</sub> CH <sub>2</sub> COOH	1.43	2250	
	H	C <sub>2</sub> H <sub>5</sub> (cis)	OCOCH <sub>3</sub>	COPh	0.14		
15	H	C <sub>2</sub> H <sub>5</sub> (trans)	OCOCH <sub>3</sub>	COPh	0.34	76600	
	H	C <sub>2</sub> H <sub>5</sub> (trans)	OPh	COCH <sub>3</sub>	4.30	5270	
	H	C <sub>2</sub> H <sub>5</sub> (trans)	OC <sub>2</sub> H <sub>5</sub>	COCH <sub>3</sub>	11.90	1670	
20	H	C <sub>2</sub> H <sub>5</sub> (trans)	OPh-p-COOH	COCH <sub>3</sub>	3.40	8727	
	H	C <sub>2</sub> H <sub>5</sub> (trans)	OPh-p-COOH	COOC <sub>2</sub> H <sub>5</sub>	2.10	8680	
	H	C <sub>2</sub> H <sub>5</sub> (trans)	OPh-p-COOH	CONHCH <sub>3</sub>	16.50		
25	H	C <sub>2</sub> H <sub>5</sub> (cis)	CON(CH <sub>2</sub> ) <sub>4</sub>	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> )	27.70	541	
	H	C <sub>2</sub> H <sub>5</sub> (cis)	COOCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> -p-COOH	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> )	4.20	299	
	H	C <sub>2</sub> H <sub>5</sub> (cis)	CON(CH <sub>3</sub> )CH <sub>2</sub> COOH	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> )	22.00	165	
30	H	C <sub>2</sub> H <sub>5</sub> (trans)	OCH <sub>2</sub> COOH	COOC <sub>2</sub> H <sub>5</sub>	-	512	
	H	C <sub>2</sub> H <sub>5</sub> (cis)	OCH <sub>2</sub> COOH	COOC <sub>2</sub> H <sub>5</sub>	-	796	
	H	n-propyl (trans)	OCH <sub>2</sub> COOM	COOC <sub>2</sub> H <sub>5</sub>	-	1504	
35	H	C <sub>2</sub> H <sub>5</sub> (trans)	OCH <sub>2</sub> CONHCH <sub>2</sub> COOH	COOC <sub>2</sub> H <sub>5</sub>	-	1000	
	H	C <sub>2</sub> H <sub>5</sub> (trans)	OCH(CH <sub>3</sub> )COOH	COOC <sub>2</sub> H <sub>5</sub>	-	346	
	H	C <sub>2</sub> H <sub>5</sub> (cis)	COOCH <sub>2</sub> COOH	SO <sub>2</sub> (p-C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> )		1554	

40 ID<sub>50</sub> is the effective dosage in micrograms per milliliter (μg/ml) for 50% inhibition of the enzyme activity two minutes after time zero. Ki is the concentration of the inhibitor (micromolar, μM) giving 50% of the control enzyme activity. k<sub>obs</sub>/I (M<sup>-1</sup> sec<sup>-1</sup>) is the second order rate constant of inactivation of the enzyme.

Table II

5

10

	R	R¹	R²	B₁	$k_{25^{\circ}\text{C}}$ / l
15	C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	1900
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH(CH <sub>3</sub> )Ph	15,000
	C <sub>3</sub> H <sub>7</sub>	H	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	5,000
20	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-CO(CH <sub>2</sub> ) <sub>2</sub> COOH-Ph)	CH <sub>2</sub> (4-Ph-Ph)	107,045
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (4-Ph-Ph)	37,000
	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OCH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (4-Ph-Ph)	44,533
25	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-NO <sub>2</sub> -Ph)	CH <sub>2</sub> Ph	6,347
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (2-Anthracene)	36,177
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(2-CH <sub>2</sub> CH-Ph)	CH <sub>2</sub> Ph	2961
30	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-CH <sub>2</sub> COOH-Ph)	CH <sub>2</sub> Ph	3175
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-CH <sub>2</sub> CH-NH <sub>3</sub> -Ph) CO <sub>2</sub> <sup>-</sup>	CH <sub>2</sub> Ph	2540
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-NHCOCH <sub>3</sub> -Ph)	CH <sub>2</sub> Ph	3503
35	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-NHCOCH <sub>2</sub> CH <sub>2</sub> COOH-Ph)	CH <sub>2</sub> Ph	2568
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-CH <sub>3</sub> CO-Ph)	CH <sub>2</sub> (4-COOH-Ph)	2807
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-CH <sub>3</sub> CO-Ph)	CH <sub>2</sub> (4-CH <sub>3</sub> CO-Ph)	5916
40	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -(2-furyl)	5223
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -(2-thienyl)	4925
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	n-C <sub>9</sub> H <sub>19</sub>	8300
45	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	(CH <sub>2</sub> ) <sub>3</sub> Ph	4537
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Naph	21,269

50

55

	R	R <sup>1</sup>	R <sup>2</sup>	R <sub>1</sub>	k <sub>25°C</sub> L <sup>-1</sup>
5	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	(CH <sub>2</sub> ) <sub>4</sub> Ph	10,894
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-Ph	CH <sub>2</sub> -(4-COOH-Ph)	1501
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -cyclohexyl	1424
10	C <sub>2</sub> H <sub>5</sub>	H	O-(4-COOH-Ph)	CH <sub>2</sub> Ph -	4000
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	2000
	CH <sub>2</sub> CH=CH <sub>2</sub>	H	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	5400
15	C <sub>3</sub> H <sub>7</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	3290
	cyclopentane		O-(4-COOH-Ph)	CH <sub>2</sub> Ph	1900
20	(R and R <sup>1</sup> combined and form the cyclopentane ring)				
25	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OCH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	1900
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> CH(CH <sub>3</sub> )Ph	2553
	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -(2-Naph)	51,000
30	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH(CH <sub>3</sub> )-(1-Naph)	12,128
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -(4-Cl-Ph)	3419
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (4-CH <sub>3</sub> -Ph)	3965
35	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (4-F-Ph)	2337
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (4-OCH <sub>3</sub> -Ph)	5162
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (4-NO <sub>2</sub> -Ph)	5075
40	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH(CH <sub>3</sub> )-(3-Cl-4-cyclo- hexyl-Ph)	20,776
	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OCH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -(3,4-methylene- dioxy-Ph)	16,984
45	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -(2-benzofuran)-	13,151
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(2-(6-COOH-Naph))	CH <sub>2</sub> Ph	5561
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (4-(4-Cl-Ph)- SO <sub>2</sub> NHCOPh)	1730

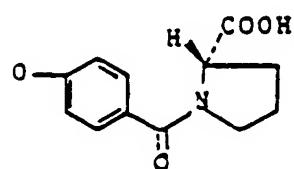
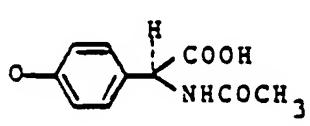
	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	k <sub>obs</sub> /I
5	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(3-CO-NHCH <sub>2</sub> -Ph) COOH	CH <sub>2</sub> Ph	3047
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(3-COOH-Ph)	CH <sub>2</sub> Ph	1763
10	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -(4-PhO-Ph) •CF <sub>3</sub> COO <sup>-</sup>	12,036
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	(CH <sub>2</sub> ) <sub>4</sub> OPh	9983
15	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	(CH <sub>2</sub> ) <sub>4</sub> CH(OH)Ph	3447
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-N(CH <sub>3</sub> ) <sub>3</sub> I <sup>-</sup> -Ph)	CH <sub>2</sub> Ph	4200
20	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	-1-imidazolyl	CH <sub>2</sub> Ph	1700
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			200
25	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>		CH <sub>2</sub> Ph	2000
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			6300
30	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>		CH <sub>2</sub> Ph	2422
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
35	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
40	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
45	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
50	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
55	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			
	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>			

Table II  
(continued)

	R	R <sup>1</sup>	R <sup>2</sup>	R <sub>1</sub>	k <sub>obs</sub> L <sup>-1</sup>
5	C <sub>2</sub> H <sub>5</sub>	H	O-(4-COOH-Ph)	Ph-4-COOH	13,563
	C <sub>3</sub> H <sub>7</sub>	C <sub>3</sub> H <sub>7</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	2,500
	allyl	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	1974
10	CH <sub>2</sub> Ph	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph	87
	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OCH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> -2-Naph	50,000
	C <sub>2</sub> H <sub>5</sub>	H	Ph-4-COOH	CH <sub>2</sub> Ph	900
15	H	OMe	Ph-4-COOH	CH <sub>2</sub> -2-Naph	1340
	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> Ph-3-CF <sub>3</sub>	55,000
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH(Et)-5-benzofuryl	750,000
20	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH(Et)-3-thienyl	78,800
	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OCH <sub>3</sub>	O-(4-COOH-Ph)	CH(nPr)Ph	75,000
	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	O-(4-COOH-Ph)	CH(Et)Ph	87,000
25	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	CO(CH <sub>2</sub> ) <sub>2</sub> COOH-Ph		
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-CH <sub>2</sub> COOH-Ph)	CH(Et)Ph	54,000
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	Cyclopentyl	—
30	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	—
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-CONH <sub>2</sub> Ph)	CH <sub>2</sub> Ph	12,500
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (3,5-diMe-4-COOH-Ph)	5,500
35	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-CONH <sub>2</sub> Ph)	CH <sub>2</sub> (3,5-diMe-4-COOH-Ph)	30,000
	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	O-(4-COOH-Ph)	CH <sub>2</sub> (3,4-diMeO-Ph)	11,300
40					

Me represents CH<sub>3</sub>

Ph represents phenyl

Pr represents propyl

Bu represents butyl

Table III

$\text{R}^2$   
 $\text{R}^1$   
 $k_{\text{obs}}/\text{I}$

	$\text{R}^2$	$\text{R}^1$	$k_{\text{obs}}/\text{I}$
15	$\text{OCH}_2\text{COOH}$	$\text{CH}_2\text{Ph}-4-\text{Ph}$	2901
	$\text{O}-(4-\text{COOH}-\text{Ph})$		4157
20	$\text{O}-(\text{allyl})$	$\text{CH}_2\text{Ph}-4-\text{Ph}$	12,545
	$-\text{l-imidazolyl}$	$\text{CH}_2\text{Ph}-4-\text{Ph}$	461
	$1-\text{triazolyl}$	$\text{CH}_2\text{Ph}-4-\text{Ph}$	2144
25	$(1-\text{methyl-tetrazol-5-yl})\text{thio}$	$\text{CH}_2\text{Ph}$	3658
	$(1-\text{H-triazol-3-yl})\text{thio}$	$\text{CH}_2\text{Ph}$	116
	$1-\text{tetrazolyl}$	$\text{CH}_2\text{Ph}$	948
30	$[2\text{H}-1-\text{pyridonyl}]$	$\text{CH}_2\text{Ph}$	357
	$\text{O-Ph-4-CO Nh}_2$	$\text{CH}_2-2-\text{Naph}(6-\text{COOH})$	40,650
	$1-\text{benzimidazolyl}$	$\text{CH}_2\text{Ph}$	69
35		$\text{CH}_2\text{Ph}$	351
	$\text{O-glyceryl}$	$\text{CH}_2\text{Ph}$	818
40	$\text{OCH}_2\text{CONH}_2$	$\text{CH}_2\text{-Ph-4-Ph}$	51,802
	$\text{NH-COOMe}$	$\text{CH}_2\text{Ph}$	496
	$\text{OCH}_2\text{-COOH}$	$\text{CH}-(\text{Et})-\text{Ph}$	5711
45	$\text{OCH}_2\text{-CONH}_2$	$\text{CH}-(\text{Et})-\text{Ph}$	102,974
	$\text{O}-(4-\text{COOH}-\text{Ph})$	$n\text{Bu}$	—
	$\text{O}-(4-\text{COOH}-\text{Ph})$	$\text{cyclopentyl}$	—
50	$\text{O-CH}_2\text{CON}(\text{Et})_2$	$\text{CH}(\text{Et})\text{Ph}$	—

Table III  
(Continued)

	<u>R<sup>2</sup></u>	<u>R<sub>1</sub></u>	<u>k<sub>obs</sub>/I</u>
5	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(2-OH)	1461
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-tBu)	21,774
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-(3-COOH)Ph)	14,727
10	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-CO-  O)	2036
15	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-CH <sub>2</sub> Ph)	8032
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(3-CH <sub>3</sub> )	6932
20	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(3,4-(CH <sub>2</sub> ) <sub>4</sub> )	62,883
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(3,4-OiMe)	20,600
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-i-Pr)	18,846
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-S(O) <sub>2</sub> Me)	3350
25	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-COMe)	5916
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-OMe-3-Me)	13,126
	O-(4-COOH-Ph)	CH <sub>2</sub> Ph(4-OCH <sub>2</sub> Ph)	12,036
30	O-(4-CH(COOH)NHAc-Ph)	CH <sub>2</sub> Ph	1676
	O-(4-CH(OH)COOH-Ph)	CH <sub>2</sub> Ph(3,4-OiMe)	17,526
	O-(3-OH-4-COOH-Ph)	CH <sub>2</sub> Ph(4-Me)	9252
35	O-(2-(CH <sub>2</sub> ) <sub>3</sub> NMe <sub>2</sub> -Ph)	CH <sub>2</sub> Ph	629
	O-(4-CH <sub>2</sub> COOH-Ph)	CH <sub>2</sub> Ph(4-Ph)	28,870

40

45

50

55

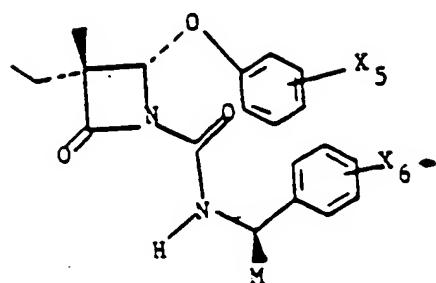
Table IV

5

10

	R	R <sup>1</sup>	R <sup>2</sup>	S	$\frac{k_{298}}{I}$
15	C <sub>2</sub> H <sub>5</sub>	-CH <sub>3</sub>	O-(4-COOH-Ph)		4376
20	C <sub>2</sub> H <sub>5</sub>	-H	O-(4-COOH-Ph)		10,066
25	C <sub>3</sub> H <sub>7</sub>	C <sub>3</sub> H <sub>7</sub>	O-(4-COOH-Ph)		1446 (lower ref.) 4324 (higher ref.)
30	C <sub>2</sub> H <sub>5</sub>	H	O-(4-COOH-Ph)	-N(CH <sub>2</sub> Ph) <sub>2</sub>	5977
35	C <sub>2</sub> H <sub>5</sub>	H	O-(4-COOH-Ph)	-OCH <sub>2</sub> -(4-COOCH <sub>2</sub> H <sub>5</sub> -Ph)	227,460
40	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	O-(4-COOH-Ph)	-OCH <sub>2</sub> -(4-COOCH <sub>2</sub> H <sub>5</sub> -Ph)	14,331
45	C <sub>2</sub> H <sub>5</sub>	H	O-(4-COOH-Ph)	-N(C <sub>2</sub> H <sub>5</sub> )(CH <sub>2</sub> Ph)	82,956
50					
55					

Table V



5

10

15

20

25

30

35

40

45

50

55

	$X_5$	M	$X_6$	$k_{obs} / l$
	4-COOH	Et	H	92,000
	4-COOH	nPr	H	152,000
	4-COOH	$CH_2OMe$	H	6,094
	$4-CH_2COOH$	Et	H	140,000
	4-COOH	Me	4-Me	47,000
	4-COOH	Et	4-Me	—
	4-COOH	$PhCH_2$	H	25,000
	$4-CH_2COOH$	nPr	H	227,000
	4-COOH	nPr	$CH_3$	—
	4-COOH	nPr	H	120,000
	4-COOH	Et	$3,4-(OCH_2O)$	—
	$4-CH_2COOH$	nBu	H	—
	4-COOH	allyl	H	—

Table VI

5

10

	$X_5$	M	$X_6$	$k_{obs}/I$
15	4-COOH	Me	H	4016
	4-COOH	Me	4-Ph	74,000
20	4-CH <sub>2</sub> COOH	Me	H	8,373
	4-COOH	Me(s)	4-Ph	49246
	4-COOH	Ph	Ph	67754
	4-COOH	Me	4-(2'-Cl-Ph)	245130
25	4-COOH	Et	4-Ph	26382
	4-COOH	Et	H	76204
	4-CO-(CH <sub>2</sub> ) <sub>2</sub> -COOMe	Me	H	37084
30	4-CO-(CH <sub>2</sub> ) <sub>2</sub> COOH	Et	H	272190
	4-COOH	nPr	H	116060
	3,5-Me <sub>2</sub> -4-COOH	Et	H	24,994
35	4-CH <sub>2</sub> COOH	Et	H	126,000
	3-OH-4-COOH	Et	H	124560
	3-CH <sub>2</sub> COOH	Me	H	5885
	4-CH=CH-COOH	Me	H	9101
40	4-COOH	CH <sub>2</sub> OMe(S)	H	6981
	4-CH <sub>2</sub> COOH	CH <sub>2</sub> OMe(S)	H	
	4-COOH	Me	-Me	10680
45	4-COOH	iPr(S)	H	4743
	4-COOH	iPr	H	177075
	4-CH <sub>2</sub> COOH	nPr	H	188,000
50	4-CH <sub>2</sub> COOH	CH <sub>2</sub> OMe(R)	H	11004
	3,5-Me <sub>2</sub> -4-COOH	nPr	H	

Table VI  
(Continued)

5

	$X_5$	H	$X_6$	$k_{obs}/l$
10	3-CH <sub>2</sub> COOH	Et	4-Me	
	4-(CH <sub>2</sub> ) <sub>2</sub> COOH	Me	H	9481
	3-CH <sub>2</sub> COOH	Et	H	81018
	4-COOH	CH <sub>2</sub> OMe(R)	H	6981
15	4-COOH	Et	3-Me	
	4-CH <sub>2</sub> COOH	Et	3-Me	
	4-CO(CH <sub>2</sub> ) <sub>2</sub> COOH	allyl	4-Me	
	4-COOH	Me	4-Me	
20	4-CH <sub>2</sub> COOH	Et	3-Cl	
	4-COOH	Et	3-Cl	
	4-COOH	allyl	3-Me	
	4-COOH	nPr	3-Me	
25	4-CH <sub>2</sub> COOH	allyl	4-Me	664,000
	3-CH <sub>2</sub> COOH	allyl	4-Me	
	4-CH <sub>2</sub> COOH	allyl	3-Me	
	4-CH <sub>2</sub> COOH	nPr	3-Me	
30	4-CO(CH <sub>2</sub> ) <sub>2</sub> COOH	nPr	4-Me	
	3-CH <sub>2</sub> COOH	allyl	H	
	3-CH <sub>2</sub> COOH	CH <sub>2</sub> OMe(S)	H	
	4-COOH	allyl	H	
35	4-CH <sub>2</sub> COOH	allyl	H	
	4-COOH	Et	4-Me	
	4-COOH	Et(S)	4-Me	
	4-COOH	allyl	4-Me	
40	4-CH <sub>2</sub> COOH	allyl	H	
	4-COOH	Et	4-Me	
	4-COOH	Et(S)	4-Me	
	4-COOH	allyl	4-Me	
45	4-COOH	nPr	4-Me	389,000
	3-CH <sub>2</sub> COOH	nPr	4-Me	
	4-CH <sub>2</sub> COOH	nPr	4-Me	557,000
50				

55

Table VI  
(Continued)

	$X_5$	H	$X_6$	$\lambda_{abs}$ (I)
	3-CH <sub>2</sub> COOH	Et	4-Cl	
	4-COOH	Et	4-Cl	
10	4-CH <sub>2</sub> COOH	Et	4-Me	
	3-CH <sub>2</sub> COOH	Et	3-Cl	
	4-COOH	allyl	3,4-methylenedioxy	
15	4-COOH	nPr	3,4-methylenedioxy	
	4-CH <sub>2</sub> COOH	allyl	3,4-methylenedioxy	605.000
	4-CH <sub>2</sub> COOH	nPr	3,4-methylenedioxy	867.000
20	3-CH <sub>2</sub> COOH	CH <sub>2</sub> COOH	4-Me	
	3-CH <sub>2</sub> COOH	nPr	H	
	4-COOH	Et	3,4-methylenedioxy	
	4-CH <sub>2</sub> COOH	Et	3,4-methylenedioxy	
25	4-COOH	Et	3,4-Me <sub>2</sub>	
	4-COOH	CH <sub>2</sub> C≡CCH <sub>3</sub>	H	
	4-CH <sub>2</sub> COOH	CH <sub>2</sub> C≡CCH <sub>3</sub>	H	
30	4-COOH	nBu	H	
	2-NO <sub>2</sub> -4-CH <sub>2</sub> COOH	Et	H	
	4-COOH	Et	4-F	
	4-COOH	Et	3-Me-4-OMe	
35				

Protocol - Enzyme Assays for the Inhibition of Human Polymorphonuclear Leukocyte Elastase Via Hydrolysis of N-t-Boc-alanyl-alanyl-prolylalanine-p-nitroanilide (Boc-AAPAN) or N-t-Boc-alanyl-prolylvaline-p-nitroanilide (Boc-AAPVN) Reagent:

0.05M TES (N-tris[hydroxymethyl]methyl-2-amino-ethanesulfonic acid) Buffer, pH 7.5.

45 0.2 mM Boc-AAPAN or Boc-AAPVN.

To prepare substrate, the solid was first dissolved in 10.0 ml DMSO. Buffer at pH 7.5 was then added to a final volume of 100 ml.

Crude extract of human polymorphonuclear leukocytes (PMN) containing elastase activity. Inhibitors (azetidinones) to be tested dissolved in DMSO just before use.

Assay Procedure:

55 To 1.0 ml of 0.2 mM Boc-AAPAN in a cuvette, 0.01-0.1 ml of DMSO with or without inhibitor was added. After mixing, a measurement was taken at 410 m $\mu$  to detect any spontaneous hydrolysis due to presence of test compound. 0.05 Milliliters of PMN extract was then added and the  $\Delta OD/min$  at 410 m $\mu$  was measured and recorded. Beckman model 35 spectrophotometer was used.

Results:

Results in Table I were reported as ID<sub>50</sub>, effective dosage in micrograms per milliliter ( $\mu\text{g}/\text{ml}$ ) for 50% inhibition of the enzyme activity 2 minutes after zero time.

- 5 Results were also expressed as K<sub>i</sub>, the micromolar concentration of the inhibitor ( $\mu\text{M}$ ) giving 50% of the control enzyme activity; or as k<sub>obs/l</sub> which is the second order rate constant in per mole per second for inactivation of the enzyme.

10 Comments:

The elastase activity in the crude PMN extract may vary from one preparation to another. A control of each new batch is run, and the volume added in the assay procedure is adjusted according to activity.

- 15 Accordingly, the compounds of Formula (I) can be used to reduce inflammation and relieve pain in diseases such as emphysema, rheumatoid arthritis, osteoarthritis, gout, bronchial inflammation, atherosclerosis, sepsis, septicemia, shock, periodontitis, cystic fibrosis, infectious arthritis, rheumatic fever and the like.

- 20 For treatment of inflammation, fever or pain, the compounds of Formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

- 25 The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

- 30 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

- 35 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadeca-ethylenoxyacetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

- 40 Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable

oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

5 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

10 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

15 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile 20 injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

25 The compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

30 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the anti-inflammatory agents are employed.

35 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between about 25 mg to about 500 mg of active ingredient.

40 It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

#### EXAMPLE 1

45

##### 1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one

50 Diazabicycloundecane (152 mg, 1 mM) was added to a mixture of 205 mg (1 mM) 4-benzyloxycarbonyl azetidin-2-one and 181 mg (1 mM) p-nitrobenzenesulfonyl chloride in 10 ml methylene chloride at room temperature. After stirring 2-1/2 hours, the orange solution was washed with water, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 64 mg (17%) of 1-p-nitrophenylsulfonyl-4-benzyloxycarbonyl azetidin-2-one.

55 NMR (CDCl<sub>3</sub>): δ 3.3 (2H, doublet, t-quartet), 4.8 (q, 1H), 5.2 (s, 2H), 7.2 (s, 5H), 8.2 (m, 4H).

#### EXAMPLE 2

1-Acetyl-3,3-dimethyl-4-acetoxazetidin-2-one

5

Step A: Preparation of 2-methyl-prop-1-enylacetate

A mixture of 72 g (1 M) isobutyraldehyde, 153 g (1.5 M) acetic anhydride and 12 g (0.125 M) potassium acetate was refluxed seven hours. The cooled reaction mixture was washed with water and stirred with 300 ml saturated NaHCO<sub>3</sub> at 0° C for 45 minutes. The organic phase was dried over K<sub>2</sub>CO<sub>3</sub> to yield a yellow oil which was distilled at atmospheric pressure to give 35.41 g (31%) of 2-methyl-prop-1-enylacetate, b.p. 122-126°.

NMR (CDCl<sub>3</sub>): δ 1.6 (s, 6H), 2.1 (s, 3H), 6.9 (milt. 1H).

15

Step B: Preparation of 3,3-dimethyl-4-acetoxazetidin-2-one

Chlorosulfonyl isocyanate (16 ml) was added to a solution of 22.8 g (0.2 M) 2-methyl prop-1-enyl acetate in 50 ml methylene chloride at 0° under nitrogen. After stirring at 0° for 20 hours, the reaction mixture was added to a mixture of 20 ml water, 90 g ice, 48 g NaHCO<sub>3</sub> and 16.6 g Na<sub>2</sub>SO<sub>3</sub> and stirred at 0° for 30 minutes. This was then extracted with 300 ml CH<sub>2</sub>Cl<sub>2</sub> and the organic phase washed with brine, dried over MgSO<sub>4</sub> and concentrated in vacuo to give 27.75 g oil which was chromatographed on silica gel in hexane/ethyl acetate to yield 2.17 g (8.5%) of 3,3-dimethyl-4-acetoxazetidin-2-one.

25 NMR (CDCl<sub>3</sub>): δ 1.2 (s, 3H), 1.3 (s, 3H), 2.2 (s, 3H), 5.6 (s, 1H).

Step C: Preparation of 1-acetyl-3,3-dimethyl-4-acetoxazetidin-2-one

30 A mixture of 283.3 mg (1.8 mM) 3,3-dimethyl-4-acetoxazetidin-2-one, 2 ml pyridine and 2 ml acetic anhydride was heated to 100° in a sealed tube for 36 hours. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel in hexane:ethyl acetate to yield 295 mg (82%) of 1-acetyl-3,3-dimethyl-4-acetoxazetidin-2-one.

35 NMR (CDCl<sub>3</sub>): δ 1.2 (s, 3H), 2.2 (s, 3H), 2.5 (s, 3H), 6.1 (s, 1H).

35

EXAMPLE 3

40

1-Acetyl-4-acetoxy-3-n-propylazetidin-2-one

45

Step A: Preparation of Pent-1-enyl acetate

A mixture of 86 g (1M) valeraldehyde, 153 g (1.5 M) acetic anhydride, and 12 g (0.125 M) potassium acetate was refluxed for 8 hours. The cooled mixture was then stirred with 100 ml saturated aqueous NaHCO<sub>3</sub> for one hour. The organic phase is separated, dried over K<sub>2</sub>CO<sub>3</sub>, and distilled at 40 mm to yield 46.15 g (45%) of pent-1-enylacetate, b.p. 89° C.

50 NMR (CDCl<sub>3</sub>): δ 1.0 (tr, 3H), 1.2-2.0 (milt., 4H), 2.1 (s, 3H), 4.7-5.6 (milt. 1H), 7.0-7.3 (milt., 1H).

55

Step B: Preparation of 4-acetoxy-3-n-propylazetidin-2-one

Eight hundred microliters of chlorosulfonyl isocyanate was added to a solution of 1.28 g (10 mM) pent-1-enyl acetate in 5 ml methylene chloride at 0° under nitrogen. After stirring at 0° 5 days, the reaction mixture was added dropwise to a mixture of 5 g ice, 1.15 ml water, 2.82 g NaHCO<sub>3</sub> and 1.0 g Na<sub>2</sub>SO<sub>3</sub> and stirred at 0° for 30 minutes. The mixture was extracted with 2 X 25 ml methylene chloride and the

combined organic phases washed with brine, dried over  $MgSO_4$ , and concentrated in vacuo. The residue was chromatographed on silica gel in hexane/ethyl acetate to yield 60 mg trans 4-acetoxy-3-n-propylazetidin-2-one (3.4%).

NMR ( $CDCl_3$ ):  $\delta$  1.0 (milt., 3H), 1.7 (milt., 4H), 2.2 (s, 3H), 3.2 (tr, 1H), 5.6 (s, 1H), 6.7 (lrs, 1H).

5

#### Step C: Preparation of 1-acetyl-4-acetoxy-3-n-propylazetidin-2-one

A mixture of 56 mg (0.33 mM) 4-acetoxy-3-propylazetidin-2-one, 1 ml acetic anhydride and 1 ml pyridine was stirred at 100° in a sealed tube for 24 hours. After concentrating in vacuo the residue was chromatographed on silica gel in hexane/ethyl acetate to yield 16 mg (23%) 1-acetyl-4-acetoxy-3-n-propylazetidine-2-one.

NMR ( $CDCl_3$ ):  $\delta$  1.0 (br tr, 3H), 1.7 (milt., 4H), 2.2 (s, 3H), 2.4 (s, 3H), 3.2 (tr, 1H), 6.1 (d, 1H).

15

#### EXAMPLE 4

#### 20 1-Acetyl-4-methylsulfonylazetidin-2-one

##### Step A: Preparation of 1-acetyl-4-methylthioazetidin-2-one

25 A mixture of 300 mg (2.6 mM) 4-methylthioazetidin-2-one, 10 ml acetic anhydride and 10 ml pyridine was stirred at 100° in a sealed tube 24 hours. After concentrating in vacuo, the residue was chromatographed on silica gel in hexane/ethyl acetate to yield 324 mg (78%) of 1-acetyl-4-methylthioazetidine-2-one. NMR ( $CDCl_3$ ):  $\delta$  2.4 (s, 3H), 2.41 (s, 3H), 3.2 (doublet-quartet, 2H), 5.1 (couplet-doublet, 1H).

30

##### Step B: Preparation of N-acetyl-4-methylsulfinylazetidin-2-one

35 A mixture of 130 mg (0.82 mM) N-acetyl-4-methylthioazetidinone and 200 mg (0.93 nM) 80% m-chloroperbenzoic acid in 5 ml methylene chloride was stirred at room temperature 5 minutes. After removing the solvent in vacuo. The residue was chromatographed on 2-2000  $\mu$ -silica gel plates in hexane/ethyl acetate to yield 57 mg (40%) of 1-acetyl-4-methylsulfinylazetidine-2-one. NMR ( $CDCl_3$ ):  $\delta$  2.4 (s, 3H), 2.6 (s, 3H), 3.5 (milt., 2H), 4.9 (milt., 1H).

40

#### EXAMPLE 5

#### 3-Azido-4-carboethoxy-1-(p-methoxyphenyl)azetidin-2-one

45 To a solution of 3.06 g of azidoacetyl chloride in 50 ml of  $CH_2Cl_2$  was added dropwise a solution of 3.57 ml of triethylamine and 5.3 g of the imine formed from ethylioxalate and p-anisidine in 50 ml  $CH_2Cl_2$ , with cooling at such a rate that the reaction temperature remained below 5°. The reaction was then stirred at room temperature for three hours and then was neutralized with 1N HCl, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic phase was dried over magnesium sulfate, filtered, and evaporated, and the crude residue was recrystallized from carbon tetrachloride/hexane to afford 3.7 g. of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)azetidine-2-one; m.p. 80-85°. NMR ( $CDCl_3$ ):  $\delta$  7.2 (d, J = 9, 2H), 6.75 (d, J = 9, 2H), 4.9 (d, J = 6, 1H), 4.6 (d, J = 6, 1H), 4.25 (q, J = 8, 2H), 3.7 (s, 3H), 1.25 (t, J = 8, 3H).

55

#### EXAMPLE 6

4-Carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one

4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one was prepared by following the same procedure as described in Example 5 but using chloroacetyl chloride and the imine formed from ethylglyoxalate and p-anisidine as the starting material. The crude product was recrystallized from ether (hexane) to give 3.1 g of 4-carboethoxy-3-chloro-1-(p-methoxyphenyl)azetidine-2-one, m.p. 99-100°. NMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (d,  $J = 9$ , 2H), 6.8 (d,  $J = 9$ , 2H), 5.1 (d,  $J = 6$ , 1H), 4.7 (d,  $J = 6$ , 1H), 4.25 (q,  $J = 7$ , 2H), 3.7 (s, 3H), 1.25 (t,  $J = 7$ , 3H).

10

EXAMPLE 715 4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one

4-Carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one was prepared by following the same procedure as described in Example 5 but using methoxyacetyl chloride as the starting material. After chromatography the compound crystallized as a white solid; m.p. 116-118°. NMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (d,  $J = 9$ , 2H), 6.75 (d,  $J = 9$ , 2H), 4.7 (d,  $J = 5$ , 1H), 4.6 (d,  $J = 5$ , 1H), 4.2 (q,  $J = 5$ , 2H), 3.7 (s, 3H), 3.5 (s, 3H), 1.2 (t,  $J = 5$ , 3H).

25

EXAMPLE 84-Carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one

30 To a solution of 17 ml of triethylamine and 5.0 g of the imine formed from ethyl glyoxalate and p-anisidine in 100 ml of refluxing 1,2-dichloroethane was added dropwise over 2 hours a solution of 16 ml of freshly distilled phenylacetyl chloride in 50 ml of dichloroethane. After refluxing for three hours the reaction was worked-up as per the 3-azidoazetidinone. The crude residue was chromatographed to yield the cis and trans isomers of 4-carboethoxy-1-(p-methoxyphenyl)-3-phenylazetidin-2-one as oils: cis: NMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (m, 7H), 6.7 (d,  $J = 9$ , 2H), 4.7 (s, 2H), 3.6 (s, 3H), 3.6 (q,  $J = 7$ , 2H), 0.7 (t,  $J = 7$ , 3H); trans: NMR ( $\text{CDCl}_3$ ):  $\delta$  7.3 (m, 7H), 6.8 (d,  $J = 9$ , 2H), 4.5 (d,  $J = 2$ , 1H), 4.45 (d,  $J = 2$ , 1H), 4.1 (q,  $J = 7$ , 2H), 3.6 (s, 3H), 1.2 (t,  $J = 7$ , 3H).

40

EXAMPLE 94-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidin-2-one

45 4-Carboethoxy-1-(p-methoxyphenyl)-3-vinylazetidin-2-one was prepared by following the same procedure as described in Example 8 but using crotonyl chloride as the reagent. After chromatography the cis and trans isomers of the compound were obtained: cis (m.p. 70-72°), NMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (d,  $J = 9$ , 2H), 6.8 (d,  $J = 9$ , 2H), 5.2-5.8 (m, 3H), 4.6 (d,  $J = 6$ , 1H), 4.2 (m, 3H), 3.7 (s, 3H), 1.2 (t,  $J = 7$ , 3H); trans (m.p. 70-72°), NMR ( $\text{CDCl}_3$ ):  $\delta$  7.25 (d,  $J = 9$ , 2H), 6.8 (d,  $J = 9$ , 2H), 5.7-6.2 (m, 1H), 5.2-5.5 (m, 2H), 4.25 (br.s., 1H), 4.2 (q,  $J = 7$ , 2H), 3.9 (dd,  $J = 1$ ,  $J_2 = 6$ , 1H), 3.75 (s, 1H), 1.25 (t,  $J = 7$ , 3H).

55

EXAMPLE 104-Carboethoxy-3-ethyl-1-(p-methoxyphenyl)azetidin-2-one

The cis and trans isomers of 4-carboethoxy-3-vinyl-1-(p-methoxyphenyl)azetidine-2-one are each hydrogenated with palladium on carbon in ethanol to yield the corresponding cis and trans isomers of 4-carboethoxy-3-ethyl-1-(p-methoxy-phenyl)azetidine-2-one.

5

EXAMPLE 1110 4-Carboethoxy-1-(p-methoxyphenyl)-3-(N-methyl-trifluoroacetamido)azetidin-2-one

A solution of 2.16 g of 3-azido-4-carboethoxy-1-(p-methoxyphenyl)-azetidine-2-one in ethanol was hydrogenated with palladium to yield 4-carboethoxy-1-(p-methoxyphenyl)-3-aminoazetidin-2-one. This amine was acylated with 1.1 ml of trifluoro acetic anhydride in 10 ml  $\text{CH}_2\text{Cl}_2$  containing 1.5 ml pyridine, followed by methylation using 1 ml dimethyl sulfate in 30 ml acetone containing 3 g potassium carbonate. After isolation, the crude product was crystallized to give 2.2 g of 4-carboethoxy-1-(p-methoxyphenyl)-3-(N-methyltrifluoroacetamido)azetidine-2-one, m.p. 102-104°.  
 NMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (d,  $J = 9$ , 2H), 6.75 (d,  $J = 9$ , 2H), 5.5 (d,  $J = 6$ , 1H), 4.7 (d,  $J = 6$ , 1H), 4.2 (q,  $J = 7$ , 2H), 3.7 (s, 3H), 3.2 (br.s., 3H), 1.2 (t,  $J = 7$ , 3H).

20

EXAMPLE 12

25

4-Carboethoxy-3-methoxyazetidin-2-one

To a solution of 1.4 g of 4-carboethoxy-3-methoxy-1-(p-methoxyphenyl)azetidine-2-one in 50 ml acetonitrile at 0° was added a solution of 8.23 g of ceric ammonium nitrate in 50 ml  $\text{H}_2\text{O}$  over 3 minutes. After stirring at 0° for 1 hour the solution was poured into 200 ml of 10% sodium sulfite and extracted with 3 X 75 ml of ethyl acetate. The combined organic extracts were washed with 10% sodium sulfite and saturated sodium chloride solutions and dried over sodium sulfate. Filtration and evaporation gave an amber oil which was recrystallized from methylene chloride:hexane to give 700 mg of 4-carboethoxy-3-methoxyazetidine-2-one; m.p. 91-92°.  
 NMR ( $\text{CDCl}_3$ ):  $\delta$  7.1 (br.s. 1H), 4.7 (dd,  $J_1 = 2$ ,  $J_2 = 5$ , 1H), 4.3 (d,  $J = 5$ , 1H), 4.15 (q,  $J = 7$ , 2H), 3.4 (s, 3H), 1.25 (t,  $J = 7$ , 3H).

Following substantially the same procedure as described in Example 12 but using an appropriate 3-substituted azetidinone compounds (a) - (f) were prepared:

(a) 4-Carboethoxy-3-chloroazetidin-2-one

NMR ( $\text{CDCl}_3$ ):  $\delta$  7.3 (br.s., 1H), 5.0 (dd,  $J_1 = 2$ ,  $J_2 = 6$ , 1H), 4.4 (d,  $J = 6$ , 1H), 4.2 (q,  $J = 7$ , 2H), 1.3 (t,  $J = 7$ , 3H).

(b) 4-Carboethoxy-3-phenylazetidin-2-one-2-(cis and trans)

NMR ( $\text{CDCl}_3$ ): cis:  $\delta$  7.2 (s, 5H), 6.4 (br.s., 1H), 4.7 (d,  $J = 6$ , 1H), 4.4 (d,  $J = 6$ , 1H), 3.7 (q,  $J = 7$ , 2H), 0.75 (t,  $J = 7$ , 3H); trans:  $\delta$  7.2 (s, 5H), 6.9 (br.s., 1H), 4.3 (br.d,  $J = 2$ , 1H), 4.1 (q,  $J = 7$ , 2H), 4.0 (d,  $J = 2$ , 1H), 1.2 (t,  $J = 7$ , 3H).

(c) 4-Carboethoxy-3-(N-methyltrifluoroacetamido) azetidin-2-one

NMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (br.s., 1H), 5.4 (d,  $J = 6$ , 1H), 4.5 (d,  $J = 6$ , 1H), 4.15 (q,  $J = 7$ , 2H), 3.2 (s, 3H), 1.2 (t,  $J = 7$ , 3H).

(d) 4-Carboethoxy-3-vinylazetidin-2-one(cis and trans)

NMR ( $\text{CDCl}_3$ ): cis:  $\delta$  7.1 (br.s., 1H), 5.2-5.8 (m, 3H), 4.0-4.4 (m, 4H), 1.25 (t,  $J = 7$ , 3H); trans:  $\delta$  7.25 (br.s., 1H), 5.0-6.2 (m, 3H), 4.1 (q,  $J = 7$ , 2H), 3.9 (d,  $J = 2$ , 1H), 3.7 (dd,  $J_1 = 2$ ,  $J_2 = 7$ , 1H), 1.2 (t,  $J = 7$ , 3H).

(e) 4-Carboethoxy-3-ethylazetidin-2-one

Cis: NMR( $\text{CDCl}_3$ ):  $\delta$  6.9 (br. s., 1H); 4.2 (m, 3H); 3.4 (dd,  $J_1 = 6$ ,  $J_2 = 8$ , 1H); 1.51 (q,  $J = 8$ , 2H); 1.2 (t,  $J = 7$ , 3H); 1.0 (t,  $J = 8$ , 3H).  
 Trans: NMR( $\text{CDCl}_3$ ):  $\delta$  6.8 (br. s., 1H); 4.2 (q,  $J = 7$ , 2H); 3.8 (d,  $J = 2$ , 1H); 3.2 (dd,  $J_1 = 2$ ,  $J_2 = 7$ , 1H); 1.8 (-dq,  $J_1 = 2$ ,  $J_2 = 8$ , 2H); 1.2 (t,  $J = 7$ , 3H); 1.0 (t,  $J = 8$ , 3H).

(f) 3-Azido-4-carboethoxyazetidin-2-one

5

EXAMPLE 134-Carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt

- 10 To a solution of 140 mg of 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one in 5 ml of pyridine at 80° was added 250 mg of sulfur trioxide pyridine complex, and the resulting mixture was stirred for 30 minutes at 80°. The solution was poured into 100 ml of 0.5 N  $\text{KH}_2\text{PO}_4$  and extracted with 2 X 25 ml of methylene chloride. The combined organic washes were back-extracted with 25 ml of  $\text{KH}_2\text{PO}_4$  solution.
- 15 The combined aqueous phases were then treated with 680 mg of tetrabutylammonium hydrogen sulfate and extracted with 3 X 50 ml of methylene chloride. After drying (sodium sulfate) and evaporation of the organic phase the crude 4-carboethoxy-3-(N-methyltrifluoroacetamido)azetidine-2-one-1-sulfonic acid tetrabutylammonium salt was chromatographed to yield an oil.
- NMR ( $\text{CDCl}_3$ ):  $\delta$  5.3 (d, J = 6, 1H), 4.7 (d, J = 6, 1H), 4.15 (q, J = 7, 2H), 3.2 (m, 11H), 0.8-1.8 (m, 31H).
- 20 Applying the same procedure as described above, the following tetrabutylammonium salts of other azetidine derivatives were prepared:
- (a) 4-Carboethoxy-3-methoxyazetidin-2-one-1-sulfonic acid tetrabutylammonium salt  
 NMR ( $\text{CDCl}_3$ ):  $\delta$  4.55 (d, J = 6, 1H), 4.5 (d, J = 6, 1H), 4.1 (q, J = 7, 2H), 3.4 (s, 3H), 3.2 (m, 8H), 0.8-1.8 (m, 31H).
- (b) 4-Carboethoxy-3-vinylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

EXAMPLE 14

30

4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenylazetidin-2-one

- 35 To a solution of 720 mg of 4-carboethoxy-3-trans-phenylazetidin-2-one in 20 ml methylene chloride at 0° were added sequentially 595 mg of p-nitrobenzenesulfonyl chloride and 0.48 ml of DBU. The solution was stirred for several hours, diluted with 50 ml of methylene chloride, washed once with water and dried over sodium sulfate. Filtration and evaporation gave a crude residue which was chromatographed to yield pure 4-carboethoxy-1-(p-nitrobenzenesulfonyl)-3-phenyl-azetidin-2-one.
- 40 NMR ( $\text{CDCl}_3$ ):  $\delta$  8.3 (d, J = 9, 2H), 8.2 (d, J = 9, 2H), 7.2 (br.s., 5H), 4.0 (q, J = 7, 2H), 3.7 (m, 2H), 1.2 (t, J = 7, 3H). Similarly prepared was the corresponding cis-3-phenyl compound. NMR ( $\text{CDCl}_3$ ):  $\delta$  8.4 (d, J = 9, 2H), 8.25 (d, J = 9, 2H), 7.2 (s, 5H), 5.0 (s, 1H), 3.7 (m, 3H), 0.85 (t, J = 7, 3H).
- Following the same procedure as described above but using appropriate reagents, the following compounds were prepared:
- (a) 4-Carboethoxy-1-(p-nitrobenzenesulfonyl)-3-vinylazetidin-2-one  
 NMR ( $\text{CDCl}_3$ ): cis:  $\delta$  8.3 (d, J = 9, 2H), 8.2 (d, J = 9, 2H), 5.2-6.0 (m, 3H), 4.0-4.6 (m, 4H), 1.2 (t, J = 7, 3H); trans:  $\delta$  8.2 (d, J = 9, 2H), 8.15 (d, J = 9, 2H), 5.2-6.0 (m, 3H), 3.9-4.4 (m, 4H), 1.25 (t, J = 7, 3H).
- (b) 4-Carboethoxy-3-ethyl-1-(p-nitrobenzenesulfonyl)azetidin-2-one  
 (c) 3-Azido-4-carboethoxy-1-(p-nitrobenzenesulfonyl)azetidin-2-one  
 (d) 4-Carboethoxy-3-chloro-1-(p-nitrobenzenesulfonyl)azetidin-2-one

EXAMPLE 15

55

4-Carboethoxy-3-phenyl-1-trifluoromethanesulfonylazetidin-2-one

To a mixture of 1.2 g of 4-carboethoxy-3-phenylazetidin-2-one and 1.2 ml of triethylamine in 25 ml of methylene chloride at 0° was added dropwise over 10 minutes 11.25 ml of a 10% solution of trifluoromethanesulfenyl chloride in ether. After stirring for several hours the solution was washed with water, dried over sodium sulfate, filtered and evaporated. The crude residue was chromatographed to yield pure 4-carboethoxy-3-phenyl-1-trifluoromethanesulfenylazetidin-2-one as an oil.

NMR ( $\text{CDCl}_3$ ):  $\delta$  7.2 (s, 5H), 4.6 (d,  $J$  = 3, 1H), 4.3 (m, 3H), 1.3 (t,  $J$  = 7, 3H).

#### EXAMPLE 16

10

#### 1-Tosyloxymethyl-3-n-Propyl-4-p-nitrophenylthioazetidin-2-one

15

#### Step A: Preparation of 3-Propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-acetoxy azetidinone, 171 mg, is refluxed with 200 mg p-nitrophenyl thiol in 10 ml benzene for 6 hours. The solution is washed 3x with aqueous  $\text{Na}_2\text{CO}_3$ , dried with  $\text{MgSO}_4$ , filtered and evaporated.

20 The residue is chromatographed on silica gel, eluting with 10:1  $\text{CHCl}_3$ -EtOAc, affording 3-Propyl-4-p-nitrophenylthioazetidin-2-one.

25

#### Step B: Preparation of 1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio azetidin-2-one

3-Propyl-4-p-nitrophenylthioazetidine-2-one, 266 mg, is stirred overnight at room temperature with 0.25 ml aqueous formalin (37%) and 17 mg  $\text{K}_2\text{CO}_3$ . Water and formaldehyde are removed in vacuo, and flushed with 2 ml pyridine. The residue is taken up in 4 ml pyridine and treated for 1 hour at room temperature with 200 mg p-toluenesulfonyl chloride. The pyridine is evaporated and replaced with 5 ml benzene. The 30 solution is washed with aqueous  $\text{H}_3\text{PO}_4$  and then aqueous  $\text{K}_2\text{HPO}_4$ , dried with  $\text{MgSO}_4$ , filtered and evaporated. The residue is chromatographed on silica gel, eluting with 25:1  $\text{CHCl}_3$ -EtOAc, providing 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylthio-azetidin-2-one.

35

#### EXAMPLE 17

40

#### 1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidin-2-one

1-Tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinylazetidin-2-one, 450 mg, is treated for 1.2 hour in 10 ml  $\text{CH}_2\text{Cl}_2$  with 172 mg m-chloroperbenzoic acid. The solution is washed with aqueous  $\text{K}_2\text{HPO}_4$ , dried with  $\text{MgSO}_4$ , filtered and evaporated, leaving pure 1-tosyloxymethyl-3-n-propyl-4-p-nitrophenylsulfinyl azetidine-2-one.

45

#### EXAMPLE 18

50

#### 1-Acetoxyethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

#### Step A: Preparation of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one

3-n-Propyl-4-acetoxy azetidinone (1.164 g, 6.58 mmole) and 1.02 g (6.58 mmole) p-nitrothiophenol were heated in a tub in the steam bath for 3.5 hours. The reaction mixture was cooled, diluted with 100 ml ethyl acetate, and the organic phase was washed with 100 ml water, 70 ml 1M  $\text{H}_3\text{PO}_4$  and 3x100 ml saturated

$K_2CO_3$ . The organic phase was dried over magnesium sulfate, filtered, and solvent removed *in vacuo* to yield 1.53 g of yellow crystals which were chromatographed on a silica gel column in chloroform-ethyl acetate (4:1) to give 359 mg (19%) of 3-n-propyl-4-p-nitrophenylthioazetidin-2-one.

NMR ( $CDCl_3$ ):  $\delta$  0.92 (tr, 3H), 1.2-1.6 (br m, 4H), 3.10 (tr, 1H), 4.91 (d, 1H), 7.0 (br s, 1H), 7.50 (d, 2H), 8.20 (d, 2H).

#### Step B Preparation of 1-Acetoxyethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one

A mixture of 273 mg (0.94 mmole) azetidinone from Step A, 26.3 mg paraformaldehyde and 178 mg (0.56 mmole) cesium carbonate was stirred in 20 ml dry tetrahydrofuran at ambient temperature 16.5 hours under nitrogen. A mixture of 430  $\mu$ l pyridine and 2.56 ml acetic anhydride was added to the reaction mixture and the stirring continued 5 more hours. The solvents were removed *in vacuo* to give 604 mg crude product which was chromatographed on a silica gel flash column in hexane-ethyl acetate 3:1. This gave 102 mg (30%) of 1-acetoxyethyl-4-p-nitrophenylthio-3-n-propylazetidin-2-one.  
NMR ( $CDCl_3$ ):  $\delta$  1.0 (tr, 3H), 1.2-1.85 (br m, 4H), 2.1 (s, 3H), 3.22 (tr, 1H), 4.95 (d, 1H), 5.18 (ABBA pattern,  $J_1 = 30H_3$ ,  $J_2 = 5H_3$ , 2H), 7.65 (d, 2H), 8.22 (d, 2H).

#### Step C Preparation of 1-Acetoxyethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one

To a solution of 46 mg (0.127 mmole) azetidinone from Step B in 4 ml  $CH_2Cl_2$  and 4 ml saturated aqueous  $NaHCO_3$  was added 27 mg (0.127 mM) 80% m-chloroperbenzoic acid and the reaction mixture stirred vigorously 15 minutes. The phases were separated and the organic phase was dried over  $MgSO_4$ , filtered and stripped to yield 57 mg crude product which was chromatographed on a 1000  $\mu$  silica gel prep TLC plate in chloroform-ethyl acetate 4:1 to yield 15 mg (31%) of 1-acetoxyethyl-4-p-nitrophenylsulfinyl-3-n-propylazetidin-2-one.  
NMR ( $CDCl_3$ ):  $\delta$  0.93 (tr, 3H), 1.2-1.8 (br m, 4H), 2.1 (s, 3H), 3.55 (tr, 1H), 4.66 (d, 1H), 5.04 (ABBA pattern,  $J_1 = 34H_3$ ,  $J_2 = 6H_3$ , 2H), 8.2 (d, 2H), 8.52 (d, 2H).

30

#### EXAMPLE 19

35

#### 4-Acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt

A solution of 82 mg (0.463 mmole) 3-propyl-4-acetoxy azetidin-2-one in 5 ml pyridine was heated to 80°. 221 Mg (1.39 mmole) sulfur trioxide-pyridine complex was added and the reaction mixture stirred at 80° one hour. It was then poured into 100 ml 0.5M  $KH_2PO_4$  (aqueous) and washed with 2x25 ml  $CH_2Cl_2$ . The combined organic washes were backwashed with 25 ml 0.5M  $KH_2PO_4$ . 157 Mg (0.463 mmole)  $Bu_4NHSO_4$  was added to the combined aqueous phases. This was extracted with 2x25 ml  $CH_2Cl_2$  and the combined extracts were dried over  $MgSO_4$ , filtered, and stripped *in vacuo* to yield 12.4 mg of an oily residue which was chromatographed on a small silica gel column, eluted first with 75 ml hexane-ethyl acetate (3:1) to remove starting material, then with 100 ml ethyl acetate:methanol (4:1) to yield 13 mg (5.7%) 4-acetoxy-3-n-propylazetidin-2-one-1-sulfonic acid tetrabutylammonium salt.  
NMR ( $CDCl_3$ ):  $\delta$  1.0 (m, 16H), 1.75 (br m, 20H), 2.16 (s, 3H), 2.90 (br s, H), 3.1 (tr, 1H), 3.3 (tr, 8H), 4.08 (br tr, 1H), 6.18 (s, 1H).

50

#### EXAMPLE 20

#### (3R,4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one

#### Step A: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 27.5 ml of diisopropylamine in 150 ml of THF at -20°C was added 73.5 ml of 2.4N n-butyl lithium in hexane. After 15 minutes, the solution was cooled to -70°C and a solution of 20 gm of (4S)-1-t-butyldimethylsilylazetidin-2-one-4-carboxylic acid in 75 mL of THF was added. The solution was warmed to -20°C for 15 minutes before a solution of 13.5 mL of methyl iodide in 20 mL of THF was added. After 30 minutes at -20 to 0°C, the reaction was diluted with 300 mL of ether and then poured into a mixture of ice and 400 mL of 1N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from hexane to give 12-15 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid.

NMR (CDCl<sub>3</sub>): δ .14 (2, 3H), .32 (s, 3H), .91 (d, 3H), .98 (s, 9H), 3.34 (dq, 1H), 3.71 (d, 1H)

10

Step B: Preparation of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid

To a solution of 13 mL of diisopropylamine in 75 mL of THF at -20°C was added 35 mL of 2.4 M n-butyl lithium in hexane. After 15 minutes the solution was cooled to -70°C and a solution of 10 gms of (3R,4S)-1-t-butyldimethylsilyl-3-methylazetidin-2-one-4-carboxylic acid in 50 mL of THF was added. The solution was warmed to -20°C for 15 minutes and a solution of 6.7 mL of ethyl iodide in 10 mL of THF was added. After 30 minutes at -20° to 0°C the reaction was diluted with ether and poured into a mixture of ice and 1 N HCl. The layers were separated and the aqueous layer extracted with ether. The ether layers were each washed with brine, dried over sodium sulfate and evaporated. The residue was crystallized from a minimum amount of hexane to give 8.8 gms of (3R,4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid.

NMR(CDCl<sub>3</sub>): δ .15 (s, 3H), .31 (s, 3H), .98 (s, 9H), 1.04 (t, 3H), 1.22 (s, 3H), 1.78 (q, 2H), 3.94 (s, 1H).

25

Step C: Preparation of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

To a solution of 13.0 gms of (3R, 4S)-1-t-butyldimethylsilyl-3-ethyl-3-methylazetidin-2-one-4-carboxylic acid in 75 mL of DMF and 15 mL of acetic acid under N<sub>2</sub> was added 23 gms of lead tetraacetate. The reaction was heated at 45-50°C for 18 hours and then poured into ice water and extracted into 2 portions of ether. The ether layers were washed with water, dilute sodium bicarbonate solution and brine, dried over sodium sulfate and evaporated to give 13 gm of crude oil containing a mixture of (3R, 4S) and (3R, 4R)-4-acetoxy-3-ethyl-3-methylazetidin-2-one. To this mixture in 50 mL of acetone was slowly added a solution of 14 gms of t-butyl 4-hydroxybenzoate in 50 mL of acetone, 5 mL of water and 29 mL of 2N sodium hydroxide. The reaction was stirred at room temperature for 64 hours and then diluted with water and extracted with 2 portions of ether. The ether layers were washed with brine, dried over sodium sulfate and evaporated. The residue was prep LC'ed with 15-25% ethylacetate-hexanes to give 6.3 gm of the high R, (4R) ether and 1.5 gm of the desired (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one.

NMR (CDCl<sub>3</sub>): δ 1.0 (t, 3H), 1.38 (s, 3H), 1.54 (s, 9H), 1.6-2.0 (m, 2H), 5.30 (s, 1H) 6.7 (brs, 1H), 6.78 (d, 2H), 7.90 (d, 2H).

45

Step D: Preparation of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one

50

To a solution of 1.5 gm of (3R, 4S)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxyazetidin-2-one in 25 mL of methylene chloride was added 1.2 mL of benzyl isocyanate, 1.4 mL of triethylamine and 10 mg of 4-dimethylaminopyridine. The reaction was stirred at room temperature for 16 hours and then evaporated. The residue was flash chromatographed eluting with 10 to 25% EtOAc Hexane to give 2.3 gm of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy)phenoxy azetidin-2-one.

NMR (CDCl<sub>3</sub>): δ .98 (t, 3H), 1.36 (s, 3H), 1.50 (s, 9H), 1.62 (m, 1H), 1.84 (m, 1H), 4.42 (d, 2H), 5.64 (s, 1H), 6.80 (brt, 1H), 7.06 (d, 2H), 7.24 (brs, 5H), 7.90 (d, 2H).

55

Step E: Preparation of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)phenoxyazetidin-2-one

To 2.3 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carbo-t-butoxy) phenoxyazetidin-

2-one in an ice bath under N<sub>2</sub> was added 5 mL of anisole and then 25 mL of precooled trifluoroacetic acid. After 1.5 hours at 0°C, the volatiles were removed in vacuo without heating and the residue flash chromatographed using hexane, then 15% EtOAc-Hexane, then 1% HOAc in 15% EtOAc-hexanes to give after ether trituration 1.8 gms of (3R, 4S)-1-(benzylaminocarbonyl)-3-ethyl-3-methyl-4-(4-carboxy)-5-phenoxyazetidin-2-one

NMR (CDCl<sub>3</sub>): δ 1.03 (t, 3H), 1.46 (s, 3H), 1.66 (m, 1H), 1.94 (m, 1H), 4.50 (d, 2H), 5.76 (s, 1H), 6.9 (brt, 1H), 7.05 (d, 2H), 7.25 (brs, 5H), 7.98 (d, 2H).

10

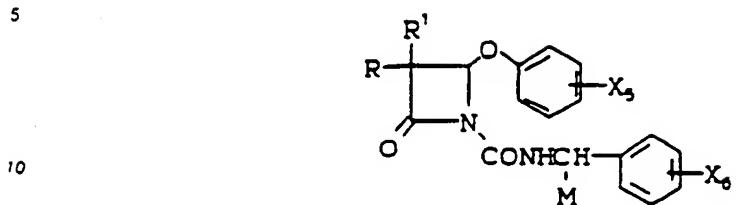
EXAMPLE 21

Starting with 3,3-diethyl-4-acetoxyazetidin-2-one as prepared in Scheme (d) followed by displacement of the acetate with the appropriate phenol and acylation of the nitrogen with the corresponding chiral isocyanate as shown in Scheme (h) and example 20, steps C-E, the following compounds were prepared. The diastereomers obtained on acylation were separated by silica gel chromatography using 10-30% ethylacetate-hexane solvent mixtures.

- 20 (4S)-3,3-diethyl-1-((R)-α-ethylbenzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.  
 NMR (CDCl<sub>3</sub>): δ 0.9 (t, 3H, J = 7Hz), 0.94 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.65 - 2.05 (m, 6H), 3.58 (s, 2H), 4.8 (q, 1H, J = 8Hz), 5.58 (s, 1H), 7.0 (d, 1H, J = 8Hz), 7.1 - 7.45 (m, 9H)
- 25 (4S)-3,3-diethyl-1-((R)-α-n-propylbenzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.  
 NMR (CDCl<sub>3</sub>): δ 0.91 (t, 3H, J = 7Hz), 0.94 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.34 (m, 2H), 1.65 - 2.05 (m, 6H), 3.57 (s, 2H), 4.88 (q, 1H, J = 7Hz), 5.58 (s, 1H), 7.0 (d, 1H, J = 7Hz) 7.1 - 7.5 (m, 9H)
- 30 (4S)-3,3-diethyl-1-((R)-α-allyl-(4-methyl)benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.  
 NMR (CDCl<sub>3</sub>): δ 0.96 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz), 1.7 - 2.1 (m, 4H), 2.32 (s, 3H), 2.57 (t, 2H, J = 7Hz), 3.58 (s, 2H), 4.95 (q, 1H, J = 7Hz), 5.14 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 7.03 (d, 1H, J = 7Hz), 7.16 (s, 4H), 7.19 (s, 4H).
- 35 (4S)-3,3-diethyl-1-((R)-α-allyl(3,4-methylenedioxy)benzylaminocarbonyl)-4-(4-carboxymethyl)-phenoxyazetidin-2-one.  
 NMR (CDCl<sub>3</sub>): δ 0.96 (t, 3H, J = 7Hz), 1.05 (t, 3H, J = 7Hz), 1.65 - 2.05 (m, 4H), 2.54 (t, 2H, J = 6Hz) 4.87 ((q, 1H, J = 7Hz), 5.05 - 5.2 (m, 2H), 5.58 (s, 1H), 5.66 (m, 1H), 5.94 (s, 2H), 6.76 (s, 3H), 6.98 (d, 1H, J = 7Hz), 7.2 (m, 4H)).
- 40 (4S)-3,3-diethyl-1-((R)-α-n-propyl(3,4-methylenedioxy)-benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.  
 NMR (CDCl<sub>3</sub>): δ 0.9 (t, 3H, J = 7Hz), 0.94 (t, 3H, J = 7Hz), 1.06 (t, 3H, J = 7Hz), 1.3 (m, 2H), 1.65 - 2.1 (m, 6H), 3.58 (s, 2H), 4.76 (q, 1H, J = 7Hz), 5.58 (s, 1H), 5.92 (s, 2H), 6.15 (s, 3H) 6.88 (d, 1H, J = 7Hz), 7.2 (m, 4H).
- 45 (4S)-3,3-diethyl-1-((R)-α-n-propyl(4-methyl)benzylaminocarbonyl)-4-(4-carboxy)phenoxyazetidin-2-one.  
 NMR (CDCl<sub>3</sub>): δ 0.91 (t, 3H, J = 7Hz), 0.98 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.32 (m, 2H), 1.65 - 2.1 (m, 6H), 2.33 (s, 3H), 4.83 (q, 1H, J = 7Hz), 5.71 (s, 1H), 6.93 (d, 1H, J = 7Hz), 7.16 (s, 4H), 7.25 (d, 2H, J = 8Hz), 8.04 (d, 2H, J = 8Hz).
- 50 (4S)-3,3-diethyl-1-((R)-α-n-propyl(4-methyl)benzylaminocarbonyl)-4-(4-carboxymethyl)phenoxyazetidin-2-one.  
 NMR (CDCl<sub>3</sub>): δ 0.9 (t, 3H, J = 7Hz), 0.93 (t, 3H, J = 7Hz), 1.07 (t, 3H, J = 7Hz) 1.28 (m, 2H), 1.7 - 2.1 (m, 6H), 2.33 (s, 2H), 3.6 (s, 2H), 4.81 (q, 1H, J = 7Hz), 5.56 (s, 1H), 6.93 (d, 1H, J = 7Hz), 7.15 (s, 4H), 7.2 (s, 4H).

## Claims

1. A compound of the formula (A)



wherein:

15 R and R' independently are C<sub>1</sub>-<sub>6</sub> alkyl or C<sub>1</sub>-<sub>6</sub> alkoxy C<sub>1</sub>-<sub>6</sub> alkyl;  
M is

- (1) hydrogen,
- (2) C<sub>1</sub>-<sub>6</sub> alkyl,
- (3) C<sub>2</sub>-<sub>5</sub> alkenyl, or
- (4) C<sub>1</sub>-<sub>6</sub> alkoxy C<sub>1</sub>-<sub>6</sub> alkyl;

20 X<sub>3</sub> is

- (1) hydrogen,
- (2) C<sub>1</sub>-<sub>6</sub> alkyl,
- (3) halo C<sub>1</sub>-<sub>6</sub> alkyl,
- (4) C<sub>2</sub>-<sub>5</sub> alkenyl,
- (5) C<sub>2</sub>-<sub>5</sub> alkynyl,
- (6) carboxy,
- (7) carboxy-C<sub>1</sub>-<sub>6</sub> alkyl,
- (8) carboxy-C<sub>1</sub>-<sub>6</sub> alkylcarbonyl,
- (9) carboxy-C<sub>1</sub>-<sub>6</sub> alkylcarbonylamino,
- (10) carboxy-C<sub>2</sub>-<sub>5</sub> alkenyl,
- (11) hydroxy-C<sub>1</sub>-<sub>6</sub> alkyl,
- (12) C<sub>1</sub>-<sub>6</sub> alkylcarbonyl,
- (13) C<sub>1</sub>-<sub>6</sub> alkylcarbonylamino, or
- (14) di-(C<sub>1</sub>-<sub>6</sub> alkyl)amino-C<sub>1</sub>-<sub>6</sub> alkyl; and

35 X<sub>4</sub> is

- (1) hydrogen,
- (2) C<sub>1</sub>-<sub>6</sub> alkyl,
- (3) halo
- (4) carboxy,
- (5) C<sub>1</sub>-<sub>6</sub> alkoxy,
- (6) phenyl,
- (7) C<sub>1</sub>-<sub>6</sub> alkylcarbonyl,
- (8) di-(C<sub>1</sub>-<sub>6</sub> alkyl)amino,
- (9) phenoxy,
- (10) methylenedioxy,
- (11) 2,3-furanyl, or
- (12) 2,3-thienyl; or

a pharmaceutically acceptable salt thereof.

40 2. A compound of Claim 1 wherein:

R and R' independently are C<sub>1</sub>-<sub>6</sub> alkyl;  
andX<sub>3</sub> is carboxy or carboxy-C<sub>1</sub>-<sub>6</sub> alkyl.

45 3. A compound of Claim 2 wherein:

M is C<sub>1</sub>-<sub>3</sub> alkyl or allyl; and  
X<sub>4</sub> is hydrogen, C<sub>1</sub>-<sub>6</sub> alkyl, or 3,4-methylenedioxy or phenyl.

4. A compound of Claim 3 wherein:

R is ethyl; and

R' is methyl or ethyl.

5. A compound of Claim 4 wherein:

5 R and R' are ethyl;

M is n-propyl;

X<sub>5</sub> is 4-carboxymethyl; and

X<sub>6</sub> is 4-methyl.

6. A pharmaceutical composition for the inhibition of human leukocyte elastase which comprises a

10 nontoxic therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

7. A composition of Claim 6 wherein:

R is ethyl;

R' is methyl or ethyl;

15 M is C<sub>1</sub>-<sub>5</sub> alkyl or allyl;

X<sub>5</sub> is carboxy or carboxy-C<sub>1</sub>-<sub>5</sub> alkyl;

and

X<sub>6</sub> is hydrogen C<sub>1</sub>-<sub>5</sub> alkyl, 3,4-methylenedioxy or phenyl.

8. A composition of Claim 7 wherein:

20 R' is ethyl;

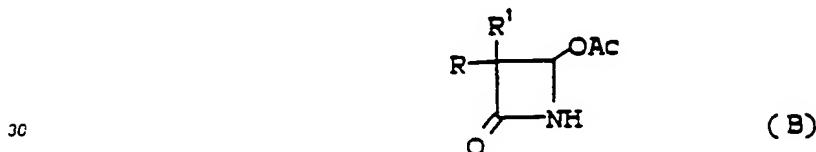
M is n-propyl;

X<sub>5</sub> is 4-carboxymethyl; and

X<sub>6</sub> is 4-methyl.

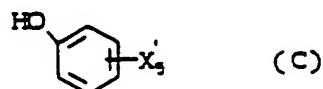
9. A process for the preparation of the compounds of Claim 1 which comprises

25 (1) reacting a compound of the following formula (B)



with a compound of the formula (C)

35



40 wherein X<sub>5</sub> is

(1) hydrogen

(2) C<sub>1</sub>-<sub>5</sub> alkyl,

(3) halo-C<sub>1</sub>-<sub>5</sub> alkyl,

(4) C<sub>2</sub>-<sub>5</sub> alkenyl,

(5) C<sub>2</sub>-<sub>5</sub> alkynyl,

(6) C<sub>1</sub>-<sub>5</sub> alkoxy carbonyl,

(7) C<sub>1</sub>-<sub>5</sub> alkoxy carbonyl-C<sub>1</sub>-<sub>5</sub> alkyl,

(8) C<sub>1</sub>-<sub>5</sub> alkoxy carbonyl-C<sub>1</sub>-<sub>5</sub> alkyl carbonyl,

(9) C<sub>1</sub>-<sub>5</sub> alkoxy carbonyl-C<sub>1</sub>-<sub>5</sub> alkyl carbonylamino,

45 (10) C<sub>1</sub>-<sub>5</sub> alkoxy carbonyl-C<sub>2</sub>-<sub>5</sub> alkenyl,

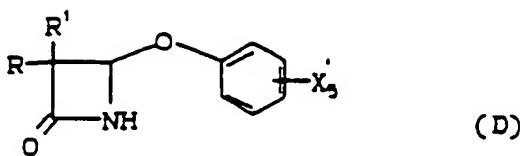
(11) hydroxy alkyl,

(12) C<sub>1</sub>-<sub>5</sub> alkyl carbonyl,

(13) C<sub>1</sub>-<sub>5</sub> alkyl carbonylamino, or

(14) di-(C<sub>1</sub>-<sub>5</sub> alkyl)amino-C<sub>1</sub>-<sub>5</sub> alkyl under basic conditions to afford a compound of the formula (D)

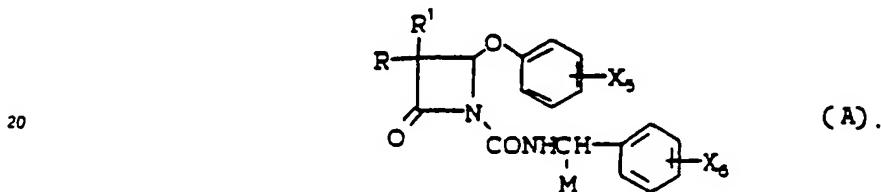
50



and (2) reacting compound (D) with a compound of the formula (E)



15 under basic conditions, and optionally converting X5' into X5, to yield the compound of the formula (A)



25 10. A process of Claim 9 wherein:

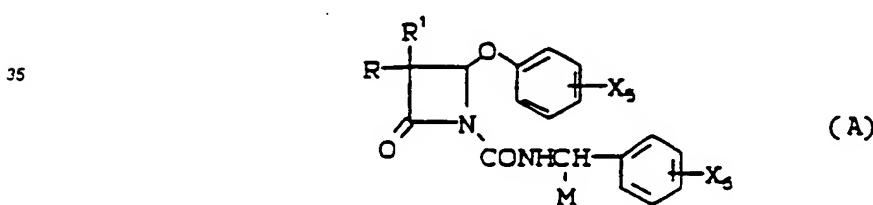
Step (1) is in the presence of an alkali metal hydroxide.

Step (2) is in the presence of a tri(C<sub>1</sub>-<sub>5</sub> alkyl)-amine; and

the conversion of X5' into X5 is accomplished in the presence of a strong acid.

Claims for the following Contracting States: ES and GR

30 1. A process for the preparation of a compound of the formula (A)



40

wherein:

R and R' independently are C<sub>1</sub>-<sub>5</sub> alkyl or C<sub>1</sub>-<sub>5</sub> alkoxy C<sub>1</sub>-<sub>5</sub> alkyl;

M is

45 (1) hydrogen,

(2) C<sub>1</sub>-<sub>5</sub> alkyl,

(3) C<sub>2</sub>-<sub>5</sub> alkenyl, or

(4) C<sub>1</sub>-<sub>5</sub> alkoxy-C<sub>1</sub>-<sub>5</sub> alkyl;

X5 is

50 (1) hydrogen,

(2) C<sub>1</sub>-<sub>5</sub> alkyl,

(3) halo C<sub>1</sub>-<sub>5</sub> alkyl,

(4) C<sub>2</sub>-<sub>5</sub> alkenyl,

(5) C<sub>2</sub>-<sub>5</sub> alkynyl,

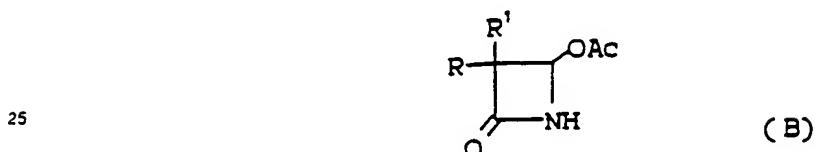
55 (6) carboxy,

(7) carboxy-C<sub>1</sub>-<sub>5</sub> alkyl,

(8) carboxy-C<sub>1</sub>-<sub>5</sub> alkylcarbonyl,

(9) carboxy-C<sub>1</sub>-<sub>5</sub> alkylcarbonylamino.

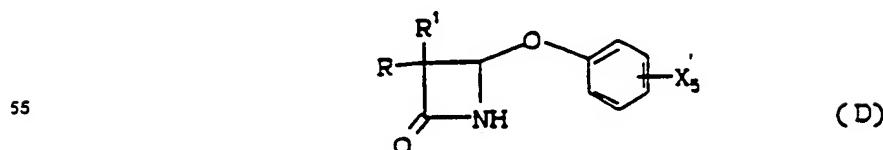
- (10) carboxy-C<sub>2</sub>-; alkenyl,  
 (11) hydroxy-C<sub>1</sub>-; alkyl,  
 (12) C<sub>1</sub>-; alkylcarbonyl,  
 (13) C<sub>1</sub>-; alkylcarbonylamino, or  
 5 (14) di-(C<sub>1</sub>-; alkyl)amino-C<sub>1</sub>-; alkyl; and  
 X<sub>6</sub> is  
 (1) hydrogen,  
 (2) C<sub>1</sub>-; alkyl,  
 (3) halo  
 10 (4) carboxy,  
 (5) C<sub>1</sub>-; alkoxy,  
 (6) phenyl,  
 (7) C<sub>1</sub>-; alkylcarbonyl,  
 (8) di-(C<sub>1</sub>-; alkyl)amino.  
 15 (9) phenoxy,  
 (10) methylenedioxy,  
 (11) 2,3-furanyl, or  
 (12) 2,3-thienyl; or  
 a pharmaceutically acceptable salt thereof which comprises  
 20 (1) reacting a compound of the following formula (B)



with a compound of the formula (C)



- 35 wherein X' is  
 (1) hydrogen  
 (2) C<sub>1</sub>-; alkyl,  
 (3) halo-C<sub>1</sub>-; alkyl,  
 (4) C<sub>2</sub>-; alkenyl,  
 40 (5) C<sub>2</sub>-; alkynyl,  
 (6) C<sub>1</sub>-; alkoxycarbonyl,  
 (7) C<sub>1</sub>-; alkoxycarbonyl-C<sub>1</sub>-; alkyl,  
 (8) C<sub>1</sub>-; alkoxycarbonyl-C<sub>1</sub>-; alkylcarbonyl,  
 (9) C<sub>1</sub>-; alkoxycarbonyl-C<sub>1</sub>-; alkylcarbonylamino,  
 45 (10) C<sub>1</sub>-; alkoxycarbonyl-C<sub>2</sub>-; alkenyl,  
 (11) hydroxalkyl,  
 (12) C<sub>1</sub>-; alkylcarbonyl,  
 (13) C<sub>1</sub>-; alkylcarbonylamino, or  
 50 (14) di-(C<sub>1</sub>-; alkyl)amino-C<sub>1</sub>-; alkyl  
 under basic conditions to afford a compound of the formula (D)



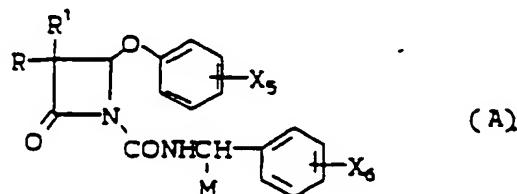
and (2) reacting compound (D) with a compound of the formula (E)

5



10

15



2. A process of Claim 1 wherein:

R and R' independently are C<sub>1</sub>-<sub>6</sub> alkyl; and

20 X<sub>5</sub> is carboxy or carboxy C<sub>1</sub>-<sub>6</sub> alkyl.

3. A process of Claim 2 wherein:

M is C<sub>1</sub>-<sub>3</sub> alkyl or allyl; and

X<sub>6</sub> is hydrogen, C<sub>1</sub>-<sub>6</sub> alkyl, or 3,4-methylenedioxy or phenyl.

4. A process of Claim 3 wherein:

25 R is ethyl; and

R' is methyl or ethyl.

5. A process of Claim 4 wherein:

R and R' are ethyl;

M is n-propyl;

30 X<sub>5</sub> is 4-carboxymethyl; and

X<sub>6</sub> is 4-methyl.

6. A process of Claim 1 wherein:

Step (1) is in the presence of an alkali metal hydroxide;

Step (2) is in the presence of a tri(C<sub>1</sub>-<sub>6</sub> alkyl)amine; and

35 the conversion of X<sub>5</sub> into X<sub>6</sub> is accomplished in the presence of a strong acid.

40

45

50

55



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application number

EP 89200864.0

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP - A1 - 0 199 630 (MERCK) * Claims 1,9 * -----	1-9	C 07 D 205/08 A 61 K 31/395
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 D 205/00
Place of search <b>VIENNA</b>			Examiner <b>JANISCH</b>
CATEGORY OF CITED DOCUMENTS			
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			
<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>			

